

LABORATORY AND CLINICAL INVESTIGATION INTO  
LOWER LIMB ISCHAEMIC PAIN, AND THE EFFECT OF  
TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION  
(TENS) ON MEASURES OF PAIN AND WALKING  
PERFORMANCE

CHRISTOPHER SEENAN

A thesis submitted in partial fulfilment of the requirements  
for the degree of Doctor of Philosophy

QUEEN MARGARET UNIVERSITY  
2013

## ABSTRACT:

---

### Aims:

The aims of this programme of research are to investigate the subjective description of ischaemic pain and to investigate the effects of TENS on lower limb ischaemic pain and walking performance in patients with Intermittent Claudication (IC).

### Methods:

Four studies were conducted: two in the laboratory and two clinical trials. *Laboratory-* The first study investigated the reliability of a method of inducing lower limb ischaemic pain in healthy volunteers, the modified Submaximal Effort Tourniquet Test (mSETT). The second investigated the effects of High Frequency TENS (HF-TENS) and Placebo TENS (P-TENS) on lower limb ischaemic pain induced using the mSETT in healthy volunteers. *Clinical-* The first clinical study investigated the effects of HF-TENS and Low Frequency TENS (LF-TENS) on measures of pain and treadmill walking performance in patients with Peripheral Arterial Disease (PAD) and IC. The second examined patients' experiences of using TENS at home for PAD and IC.

### Results:

The mSETT was found to have good test-retest reliability and induce pain similar in quality to that experienced by patients with IC. The pain experience induced with the mSETT was reduced by both HF- and P-TENS compared to baseline. HF-TENS however was more effective compared to P-TENS in this regard, prolonging time to pain threshold and tolerance whilst reducing the levels of pain reported throughout. In patients with PAD and IC, HF and LF-TENS interventions were found to increase maximum walking distance on a treadmill compared to P-TENS. HF-TENS was also found to increase pain-free walking distance. The experience of using TENS in daily life was characterised by feelings of both benefit and disappointment. This was interpreted through the following themes: (i) 'masking, but not taking the pain away' and (ii) 'walking further, but not far enough'.

### Conclusions:

The mSETT is a reliable method of inducing lower limb, ischaemic pain in healthy volunteers and could be useful for the purposes of pre-clinical analgesic trials and investigation of the ischaemic pain experience. HF-TENS was found to reduce mSETT pain indicating hypoalgesic effects of TENS in experimentally induced, lower limb ischaemic pain. HF and LF-TENS have potential as interventions that increase walking performance for patients with IC. If using TENS at home for IC, expectations of treatment effect need to be managed to avoid disappointment and feelings of frustration.

**Keywords:** Peripheral Arterial Disease, Intermittent Claudication, Transcutaneous Electrical Nerve Stimulation, Ischaemic pain, Experimental pain

## ACKNOWLEDGEMENTS:

---

Thanks are due to the following people for their assistance and support during the completion of this thesis:

My supervisory team: Dr Chee-Wee Tan, Prof Tom Mercer and Prof Jill Belch who have been inspiring and supportive. Working with such a knowledgeable team has been invaluable. Special thanks particularly to Stephen McSwiggan and Linda Orr for their help and support with clinical data collection. Thanks also to Dr Patricia Roche who had the original idea for the project and has supported me since my undergraduate dissertation.

Thanks to all the participants who gave up their time for the studies and without whom the research would not have been possible and thanks to Queen Margaret University for awarding me a PhD Studentship.

To all my colleagues within the School of Health Sciences, Queen Margaret University, and the School of Health and Life Sciences, Glasgow Caledonian University. Special thanks to all my fellow PhD survivors who have provided much-needed forum for discussion and an empathetic ear. Special thanks to Andrea Coda- always ready for a coffee and some words of advice.

Thanks to Mum and Dad for all of your patience and never ending moral support. You have taught me most of the things I know to be true.

Thanks to Peter, Niall, Brendan and Martin for your unwavering brotherly support and encouragement.

Thanks to Bill, Elaine, David, Dave, Ralph and all other friends and family for understanding and encouraging my temporary reclusive personality.

Lastly, thanks to Jill. You have endured the good and bad and always given me love, support and encouragement. Without you I wouldn't have managed to get through this and I definitely wouldn't be so happy.

I would like to dedicate this work to the memories of my grandfather, Rev. Colin William Ryland: an incredible man and a constant source of motivation and inspiration in every aspect of my life.

## PUBLICATIONS:

---

### REFEREED JOURNALS:

---

**Seenan, C.,** Roche, P.A., Tan, C-W., Mercer, T. 2012. Modification of experimental, lower limb ischemic pain with Transcutaneous Electrical Nerve Stimulation. *Clinical Journal of Pain*. Vol:28(8); pp 693-699

### PRESENTATIONS:

---

**Seenan, C.,** McSwiggan, S.J., Roche, P.A., Tan, C-W., Mercer, T., Belch, J.F. 2013. Pain Self-Efficacy: A key variable in Walking Performance for patients with Peripheral Arterial Disease and Intermittent Claudication. Poster Presented at: *Scottish Pain Research Community (SPaRC) 3<sup>rd</sup> Annual Scientific Meeting*, Dundee, UK. 28<sup>th</sup> March 2013

**Seenan, C.,** McSwiggan, S.J., Roche, P.A., Tan, C-W., Mercer, T., Belch, J.F. 2012. McGill Pain Questionnaire Descriptions of Lower Limb Ischaemic Pain in Clinical and Laboratory Settings. Poster Presented at: *The 14<sup>th</sup> World Congress on Pain*, Milan, Italy 27<sup>th</sup>-31<sup>st</sup> August 2012

**Seenan, C.,** McSwiggan, S.J., Roche, P.A., Tan, C-W., Mercer, T., Belch, J.F. 2012. Improved treadmill walking with Transcutaneous Electrical Nerve Stimulation in patients with Peripheral Arterial Disease and Intermittent Claudication. *British Journal of Pain*. Vol:6(2) Suppl. pp 80

**Seenan, C.,** McSwiggan, S.J., Roche, P.A., Tan, C-W., Mercer, T., Belch, J.F. 2012. 'Grin and bear it': patients' experiences of living with Peripheral Arterial Disease and using Transcutaneous Electrical Nerve Stimulation for Intermittent Claudication. *British Journal of Pain*. Vol:6(2) Suppl. pp 81

**Seenan, C.,** Santos, D., Calcraft, J., Weddell, A. Roche, P. A., 2008. Early development of a Lower Limb Ischaemic Pain Test in healthy volunteers using the McGill Pain Questionnaire. Poster Presented at: *The 12<sup>th</sup> World Congress on Pain*, Glasgow, UK 17<sup>th</sup> - 22<sup>nd</sup> August 2008.

Roche, P.A., Santos, D., **Seenan, C.,** Snijder, J., Weddell, A., Sweers, I., Ham, E. 2007. A Model of Ischaemic Pain in the Lower Limb and Its Modification with TENS: Preliminary Results. In: *Physiotherapy*, 93, Supplement 1, 2 June 2007, pp S1-S802. World Congress on Physical Therapy 2007. Vancouver, Canada - Abstracts



## CONTENTS:

---

<b>ABSTRACT:</b> .....	<b>II</b>
<b>ACKNOWLEDGEMENTS:</b> .....	<b>III</b>
<b>PUBLICATIONS:</b> .....	<b>IV</b>
REFEREED JOURNALS: .....	IV
PRESENTATIONS: .....	IV
<b>LIST OF FIGURES:</b> .....	<b>12</b>
<b>LIST OF TABLES:</b> .....	<b>15</b>
<b>ABBREVIATIONS:</b> .....	<b>17</b>
<b>CHAPTER 1: INTRODUCTION</b> .....	<b>19</b>
1.1: AIM OF CHAPTER 1: .....	19
1.2: INTRODUCTION TO THE THESIS: .....	19
1.2.1: <i>The Clinical Problem:</i> .....	20
1.2.2: <i>Subjective Description of IC Pain:</i> .....	21
1.2.3: <i>Current Management of IC:</i> .....	22
1.2.4: <i>Possible Adjunct to Current Treatment of IC:</i> .....	22
1.2.5: <i>Laboratory Investigations of Pain:</i> .....	23
1.2.6: <i>Laboratory Ischaemic Pain:</i> .....	23
1.2.7: <i>Summary:</i> .....	24
1.3: RESEARCH QUESTIONS ADDRESSED IN THIS THESIS: .....	25
1.4: AIMS AND OBJECTIVES: .....	25
1.5: STRUCTURE OF THESIS: .....	27
1.6: SUMMARY OF THESIS CONTENT: .....	29
1.6.1: <i>Chapter 2: Peripheral Arterial Disease (PAD) and Intermittent Claudication (IC) ..</i>	29
1.6.2: <i>Chapter 3: Pain</i> .....	29
1.6.3: <i>Chapter 4: Transcutaneous Electrical Nerve Stimulation (TENS)</i> .....	29
1.6.4: <i>Chapter 5: Laboratory-Induced Pain</i> .....	29
1.6.5: <i>Chapter 6: Literature Review Summary and Rationale</i> .....	30
1.6.6: <i>Chapter 7: Experiment One - Test-Retest Reliability of the modified SETT</i> .....	30
1.6.7: <i>Chapter 8: Experiment Two - The Effects of TENS on mSETT-Induced Pain</i> .....	30
1.6.8: <i>Chapter 9: Experiment Three - The Effects of TENS on Pain and Walking</i>	
<i>Performance in Patients with PAD and IC</i> .....	30
1.6.9: <i>Chapter 10: Comparison of Experimental and Clinical Ischaemic Pain</i> .....	30
1.6.10: <i>Chapter 11: A Pilot Investigation into Patients' Experiences of Using TENS for</i>	
<i>Daily Life with PAD and IC</i> .....	30
1.6.11: <i>Chapter 12: General Discussions and Conclusions</i> .....	31
<b>CHAPTER 2: PERIPHERAL ARTERIAL DISEASE (PAD) AND INTERMITTENT CLAUDICATION (IC)</b>	
.....	<b>32</b>
2.1: AIM OF CHAPTER 2: .....	32
2.2: PERIPHERAL ARTERIAL DISEASE: .....	32
2.3: INTERMITTENT CLAUDICATION .....	33
2.3.1: <i>IC Pain:</i> .....	34

2.3.2: <i>Psychosocial Aspects of IC:</i>	36
2.4: MANAGEMENT OF PAD AND IC:	39
2.4.1: <i>Exercise Therapy:</i>	41
2.4.2: <i>Pharmacological Therapy:</i>	44
2.4.2.1: Cilostazol:	44
2.4.2.2: Pentoxifylline:	44
2.4.2.3: Naftidrofuryl:	45
2.4.2.4: Carnitine and Propionyl-L-Carnitine:	45
2.4.2.5: Lipid lowering drugs (Statins):	46
2.4.3: <i>Limitations with the Current Management of PAD and IC:</i>	46
2.4.3.1: Adherence to Exercise Therapy:	46
2.4.3.2: Side Effects, Cost-Effectiveness and Mechanisms of Action of Pharmacological Therapy:	48
2.4.4: <i>Summary of the Management of PAD and IC:</i>	49
2.5: CURRENT HEALTHCARE PROVISION FOR THOSE WITH PAD AND IC IN THE UK:	50
2.6: CONCLUSION:	52
2.7: CHAPTER 2 SUMMARY:	53
<b>CHAPTER 3: PAIN</b>	<b>54</b>
3.1: AIM OF CHAPTER 3:	54
3.2: DEFINITIONS OF PAIN:	54
3.3: THEORIES OF PAIN:	54
3.4: CLASSIFICATION OF PAIN:	57
3.5: MEASUREMENT OF PAIN:	58
3.5.1: <i>The Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS):</i>	58
3.5.2: <i>The McGill Pain Questionnaire (MPQ):</i>	59
3.5.2.1: Psychometric Properties:	62
Reliability:	62
Validity:	62
Sensitivity:	63
3.5.2.2: Describing Pain Syndromes with the MPQ:	63
3.5.3: <i>The Short-Form MPQ (SF-MPQ):</i>	65
3.5.4: <i>Summary:</i>	66
3.6: PSYCHOSOCIAL ASPECTS OF PAIN:	67
3.6.1: <i>Pain Catastrophising:</i>	68
3.6.2: <i>Pain-Related Fear:</i>	68
3.6.3: <i>Perceived Control and Pain Self-Efficacy:</i>	69
3.6.4: <i>Helplessness and Depression:</i>	69
3.6.5: <i>Summary:</i>	70
3.7: CONCLUSION:	70
3.8: CHAPTER 3 SUMMARY:	71
<b>CHAPTER 4: TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS)</b>	<b>72</b>
4.1: AIM OF CHAPTER 4:	72
4.2: NON-PHARMACEUTICAL INTERVENTIONS FOR IC:	72
4.2.1: <i>TENS:</i>	72
4.3: HISTORY OF TENS:	73
4.4: TENS MECHANISMS OF ACTION:	73
4.4.1: <i>High-Frequency TENS (HF-TENS):</i>	74
4.4.2: <i>Low-Frequency TENS (LF-TENS):</i>	74
4.5: EVIDENCE FOR THE NEUROPHYSIOLOGICAL MECHANISMS OF TENS:	75

4.5.1: <i>Animal Pain Models</i> :	76
4.5.2: <i>Human Pain Models</i> :	77
4.5.3: <i>Summary</i> :	79
4.6: EVIDENCE FOR THE USE OF TENS FOR PAIN RELIEF:	80
4.6.1: <i>Summary</i> :	85
4.7: CONCLUSION:	85
4.8: CHAPTER 4 SUMMARY:	86
<b>CHAPTER 5: LABORATORY-INDUCED ISCHAEMIC PAIN AND TENS</b>	<b>87</b>
5.1: AIM OF CHAPTER 5:	87
5.2: INVESTIGATING PAIN IN CLINICAL POPULATIONS AND LABORATORY-INDUCED PAIN:	87
5.3: A PRE-CLINICAL MODEL OF IC PAIN:	88
5.3.1: <i>Variations of the SETT</i> :	89
5.4: TENS AND LABORATORY-INDUCED ISCHAEMIC PAIN:	97
5.4.1: <i>Systematic Review of TENS for Ischaemic Pain in Healthy Volunteers</i> :	97
5.4.1.1: Methodological Considerations:	97
5.4.1.2: Search Strategy:	98
5.4.1.3: Inclusion Criteria and Methodological Assessment:	99
5.4.1.4: Data Analysis:	100
5.4.1.5: Results:	100
Methodological Quality:	100
General Outcomes:	103
Comparison Against Control/Placebo/Sham:	103
Methodological Differences and Outcomes:	104
SETT Method	104
Pain Measurement	106
TENS Parameters	106
5.4.1.6: Summary:	112
5.5: LOWER LIMB LABORATORY-INDUCED ISCHAEMIC PAIN:	117
5.5.1: <i>Pilot Studies of Lower Limb Laboratory-Induced Ischaemic Pain</i> :	117
5.5.2: <i>TENS for Laboratory-Induced Lower Limb Ischaemic Pain</i> :	120
5.5.3: <i>Future Directions</i> :	120
5.6: CONCLUSION:	120
5.7: CHAPTER 5 SUMMARY:	121
<b>CHAPTER 6: LITERATURE REVIEW SUMMARY AND STUDY RATIONALE</b>	<b>122</b>
6.1: AIM OF CHAPTER 6:	122
6.2: SUMMARY OF LITERATURE REVIEW AND RESEARCH QUESTIONS:	122
6.3: AIMS AND OBJECTIVES OF THIS PROJECT:	123
6.4: CHAPTER 6 SUMMARY:	125
<b>CHAPTER 7: EXPERIMENT ONE - TEST-RETEST RELIABILITY OF THE MODIFIED SETT (MSETT)</b>	<b>126</b>
7.1: AIM OF CHAPTER 7:	126
7.2: METHOD:	126
7.2.1: <i>Design</i> :	126
7.2.2: <i>Participants</i> :	127
7.2.3: <i>Measures</i> :	127
7.2.3.1: Pain:	127
7.2.3.2: Psychosocial:	128
7.2.3.3: Physiological:	128
7.2.4: <i>Study Procedure</i> :	129

7.2.4.1: Introduction and Baseline Data Collection: .....	129
7.2.4.2: Familiarisation Session: .....	130
7.2.4.3: mSETT Procedure: .....	130
Rest Period: .....	132
Desanguination:.....	133
Occlusion of Blood Flow: .....	133
Submaximal Effort Exercise: .....	134
Period of Induced Pain: .....	136
Release Occlusion of Blood Flow: .....	138
7.2.5: <i>Statistical Analysis</i> : .....	138
7.3: RESULTS: .....	139
7.4: DISCUSSION:.....	144
7.5: IMPLICATIONS AND CONCLUSIONS:.....	145
7.6: CHAPTER 7 SUMMARY:.....	145
<b>CHAPTER 8: EXPERIMENT TWO - THE EFFECTS OF TENS ON MSETT-INDUCED PAIN .....</b>	<b>146</b>
8.1: AIM OF CHAPTER 8: .....	146
8.2: POWER CALCULATION: .....	146
8.3: METHOD: .....	147
8.3.1: <i>Design</i> : .....	147
8.3.2: <i>Participants</i> :.....	148
8.3.3: <i>Procedure</i> :.....	148
8.3.4: <i>TENS Procedure</i> : .....	149
8.3.5: <i>Measures</i> : .....	151
8.3.6: <i>Statistical Analysis</i> :.....	152
8.4: RESULTS: .....	155
8.4.1: <i>Pain Intensity</i> :.....	156
8.4.1.1: Pain Threshold, Tolerance and Endurance: .....	156
8.4.1.2: 21-NRS Scores: .....	159
8.4.2: <i>Pain Quality</i> : .....	164
8.5: DISCUSSION:.....	167
8.6: CONCLUSIONS:.....	169
8.7: CHAPTER 8 SUMMARY:.....	170
<b>CHAPTER 9: EXPERIMENT THREE - THE EFFECTS OF TENS ON PAIN AND WALKING PERFORMANCE IN PATIENTS WITH PAD AND IC .....</b>	<b>171</b>
9.1: AIM OF CHAPTER 9: .....	171
9.2: POWER CALCULATION: .....	171
9.2.1: <i>Clinically Significant Difference</i> : .....	171
9.3: METHODS: .....	172
9.3.1: <i>Design</i> : .....	172
9.3.2: <i>Participants</i> :.....	172
9.3.2.1: Inclusion and Exclusion Criteria: .....	175
9.3.3: <i>Procedure</i> :.....	176
9.3.3.1: Cardiac Assessment: .....	177
9.3.3.2: Initial Interview and Descriptive Data: .....	177
9.3.3.3: Familiarisation Session: .....	177
9.3.3.4: Rest Period and ABPI: .....	178
9.3.3.5: Gardner Treadmill Test:.....	178
Validity and Reliability: .....	179
9.3.3.6: MPQ: .....	180
9.3.4: <i>TENS Procedure</i> : .....	180

9.3.5: Statistical Analysis: .....	181
9.4: RESULTS: .....	184
9.4.1: Participants:.....	184
9.4.2: Within Group Profiles (HF-TENS and LF-TENS vs. P-TENS): .....	186
9.4.3: Between Group Profiles (HF-TENS vs. LF-TENS):.....	186
9.4.4: Pooled treadmill analysis:.....	190
9.4.5: Interrelationships between variables: .....	191
9.4.5.1: Descriptive and Baseline Measures:.....	191
9.4.5.2: Experimental Measures:.....	191
9.4.6: Predictors of ACD and Change in ACD:.....	194
9.4.6.1: ACD .....	194
9.4.6.2: Change in ACD .....	194
9.4.7: Summary of Analysis and Results:.....	194
9.5: DISCUSSION:.....	197
9.5.1: TENS and increased walking performance:.....	198
9.5.2: Frequency parameters of TENS and walking performance:.....	202
9.5.3: Pooled Analysis of TENS:.....	203
9.5.4: Interrelationships between measures: .....	205
9.5.5: Predictors of Walking Performance:.....	210
9.6: CONCLUSIONS:.....	215
9.7: CHAPTER 9 SUMMARY:.....	216
<b>CHAPTER 10: COMPARISON OF EXPERIMENTAL AND CLINICAL ISCHAEMIC PAIN .....</b>	<b>217</b>
10.1: AIM OF CHAPTER 10:.....	217
10.2: METHODS: .....	218
10.2.1: Design:.....	218
10.2.2: Participants:.....	218
10.2.3: Study Procedure:.....	218
10.2.4: Measures: .....	218
10.2.5: Statistical Analysis:.....	218
10.3: RESULTS: .....	220
10.3.1: Participants:.....	220
10.3.2: Descriptive Qualities:.....	220
10.3.3: Intensity:.....	221
10.3.4: Overall pain experience: .....	224
10.3.4.1: PRI (S) .....	224
10.3.4.2: PRI (R).....	224
10.4: DISCUSSION:.....	227
10.4.1: IC Pain: .....	227
10.4.2: Clinical and Laboratory-Induced Ischaemic Pain:.....	232
10.4.3: Limitations to this Approach for Validation of the mSETT: .....	235
10.5: CHAPTER 10 SUMMARY:.....	237
<b>CHAPTER 11: AN INVESTIGATION INTO PATIENTS' EXPERIENCES OF USING TENS FOR DAILY LIFE WITH PAD AND IC.....</b>	<b>238</b>
11.1: AIM OF CHAPTER 11:.....	238
11.2: METHOD: .....	238
11.2.1: Methodological Justification: .....	238
11.2.2: Design: .....	242

11.2.3: <i>Participants</i> :	242
11.2.3.1: Inclusion and Exclusion Criteria:	243
11.2.4: <i>Procedure</i> :	244
11.2.4.1: Initial Meeting:	244
11.2.4.2: Second Meeting:	244
11.2.4.3: Questionnaires:	246
11.2.4.4: Analysis:	246
Coding:	246
Category	246
Theme:	247
Sub-Theme	247
Process of Analysis:	247
11.3: FINDINGS:	249
11.3.1: <i>Participants</i> :	249
11.3.2: <i>Methodological Considerations</i> :	252
11.3.3: <i>Themes</i> :	253
11.3.3.1: The experience of living with PAD and IC:	254
Frustration:	254
Pain:	256
Limited Physical and Social Functioning:	258
Acceptance, adaptation and control of the pain and disease:	259
Knowledge and Understanding:	263
11.3.3.2: TENS for daily life with PAD and IC:	267
Pain:	267
Control:	267
Expectations:	267
Usability:	269
Physical and Social Functioning:	271
11.3.4: <i>Summary</i> :	272
11.4: DISCUSSION:	273
11.4.1: <i>Background</i> :	273
11.4.2: <i>Themes</i> :	276
11.4.2.1: Frustration:	276
11.4.2.2: Pain:	276
11.4.2.3: Limited physical and social functioning	278
11.4.2.4: Acceptance, adaptation and control of the pain and disease	278
11.4.2.5: Knowledge and understanding:	280
11.4.3: <i>Strengths and Limitations of the Study</i> :	282
11.5: CHAPTER 11 SUMMARY:	285
<b>CHAPTER 12: GENERAL DISCUSSIONS AND CONCLUSIONS:</b>	<b>286</b>
12.1: AIM OF CHAPTER 12:	286
12.2: SUMMARY OF KEY FINDINGS FROM THE CURRENT PROJECT:	288
12.3: GENERAL DISCUSSIONS:	291
12.3.1: <i>General Findings Related to Research Aim 1</i> :	291
12.3.1.1: The pain experience of IC is characterised by specific descriptive adjectives and the mSETT could provide an adequate laboratory representation:	291
12.3.1.2: The mSETT is a reliable method of inducing lower limb ischaemic pain in a small sample of volunteers	293
12.3.1.3: Psychosocial variables correlate with walking performance in patients with IC	294
12.3.1.4: Living with PAD and IC is characterised by feelings of frustration:	296
12.3.1.5: Summary:	297
12.3.2: <i>General Findings Related to Research Aim 2</i> :	298
12.3.2.1: TENS decreases mSETT-induced pain and increases walking performance in PAD and IC:	298
12.3.2.2: TENS has no effect on pain intensity despite increasing walking distance:	300
12.3.2.3: Summary:	301
12.3.3: <i>Clinical implications of the present findings</i> :	301

12.3.3.1: Assessment and interventions that address the psychosocial aspects of PAD and IC:.....	302
12.3.3.2: The mSETT as a method of inducing ischaemic pain in the lower limb of healthy volunteers and as a pre-clinical model of IC pain: .....	303
12.3.3.3: Further evidence of the hypoalgesic effects of TENS and a possible new application in IC pain: .....	304
<b>12.3.4: Limitations of the studies included in this thesis: .....</b>	<b>305</b>
<b>12.3.5: Future Directions: .....</b>	<b>307</b>
12.3.5.1: Further laboratory investigations of mSETT-induced pain and the effects of TENS: .....	307
12.3.5.2: Further clinical investigation of IC pain and the effects of TENS: .....	308
<b>12.4: CONCLUSION: .....</b>	<b>310</b>
<b>CHAPTER 13: REFERENCES: .....</b>	<b>312</b>
<b>CHAPTER 14: APPENDICES .....</b>	<b>350</b>
14.1: APPENDIX 1: DETAILS OF SEARCH RESULTS AND REASONS FOR EXCLUSION .....	350
14.2: APPENDIX 2: STANDARDISED DATA EXTRACTION TABLES .....	354
14.3: APPENDIX 3: MODIFIED JADAD SCALE .....	365
14.4: APPENDIX 4: LABORATORY STUDY INFORMATION SHEET .....	366
14.5: APPENDIX 5: LABORATORY STUDY EXCLUSION CRITERIA QUESTIONNAIRE .....	369
14.6: APPENDIX 6: LABORATORY STUDY CONSENT FORM .....	371
14.7: APPENDIX 7: RANDOMISATION PROCEDURE FOR TREADMILL STUDY .....	373
14.8: APPENDIX 8: TREADMILL STUDY INFORMATION SHEET .....	374
14.9: APPENDIX 9: TREADMILL STUDY CONSENT FORM .....	380
14.10: APPENDIX 10: TREADMILL STUDY QUESTIONNAIRES.....	381
14.11: APPENDIX 11: GARDNER TREADMILL PROTOCOL .....	391
14.12: APPENDIX 12: TENS DAILY USE STUDY INVITATION LETTER .....	397
14.13: APPENDIX 13: TENS DAILY USE STUDY INFORMATION SHEET.....	399
14.14: APPENDIX 14: TENS DAILY USE STUDY CONSENT FORM .....	403
14.15: APPENDIX 15: TENS DAILY USE STUDY PARTICIPANT REPLY SHEET.....	404
14.16: APPENDIX 16: TENS DAILY USE STUDY TENS INSTRUCTIONS.....	405
14.17: APPENDIX 17: FOCUS GROUP STATEMENTS.....	406
14.18: APPENDIX 18: TENS DAILY USE STUDY QUESTIONNAIRES.....	407
14.19: APPENDIX 19: FOCUS GROUP ANALYSIS.....	427
<b>CHAPTER 15: RELEVANT PUBLICATIONS .....</b>	<b>446</b>

## LIST OF FIGURES:

Figure 1.1: Flow diagram of thesis structure. The additional study not discussed in section 1.4 above will be introduced and discussed in Chapter 11. This is due to its nature as a follow-up study rather than a part of the initial project plan. ....	28
Figure 2.1: The cycle of disability and the benefits of exercise training in patients with PAD and IC. Reproduced with permission from Milani and Lavie (2007). ....	43
Figure 5.1: PRISMA diagram detailing the outcome of the search strategy. Details of studies screened and reasons for exclusion are detailed in Appendix 1 and Table 5.4. ....	101
Figure 7.1: Experiment procedure. ....	129
Figure 7.2: Modified Submaximal Effort Tourniquet Test (mSETT) procedure. Key: 1-Rest Period; 2-Limb Elevated; 3-Desanguination; 4-Cuff Inflated; 5-Standing in test position and backpack on; 6-Single-leg heel raise exercises; 7-Backpack removed; 8-21-NRS at irregular intervals; 9-Cuff Deflated over 2 mins. ....	131
Figure 7.3: Participant relaxation, supine on plinth ....	132
Figure 7.4: Equipment placed on the participant's non-dominant lower limb with the sphygmomanometer cuff proximal to the popliteal crease.....	132
Figure 7.5: Desanguination of the participant's limb with the equipment in place.....	133
Figure 7.6: Participant standing next to plinth with cuff in place, dominant leg on weighing scales and support on either side.....	134
Figure 7.7: The weighted backpack on the participant's back .....	135
Figure 7.8: Heel raise exercise. Contraction phase with the non-dominant (left) heel raised off the ground. The dominant heel is raised in order to maintain minimal contact with the scales and ensure the leg being tested is performing maximal weight bearing. ....	135
Figure 7.9: Heel raise exercise- relax phase with the non-dominant (left) heel returned to the ground.....	136
Figure 7.10: Experimental position with the participant's non-dominant knee 'unlocked' i.e. in a small amount of knee flexion during the experimental procedure .....	137
Figure 7.11: Individual participant data for time taken to report Pain Threshold (secs) in both trials. ....	141
Figure 7.12: Individual participant data for time taken to report Pain Tolerance (secs) in both trials. ....	141
Figure 7.13: Individual participant data for Pain Endurance (secs) in both trials. ....	142
Figure 7.14: Scatterplot of time taken to report pain threshold in both trials. Line represents $y=x$ . ....	142
Figure 7.15: Scatterplot of time taken to report pain tolerance in both trials. Line represents $y=x$ . ....	143
Figure 7.16: Scatterplot of pain endurance in both trials. Line represents $y=x$ . ....	143
Figure 8.1: Flow diagram of participant study progression.....	148
Figure 8.2: Common electrode placement sites with one electrode immediately superior and one immediately inferior to the Gastrocnemius muscle belly on the posterior aspect of the lower limb .....	149
Figure 8.3: The experimental set up including an example of the stimulation sites just visible beneath the elastic bandage .....	150
Figure 8.4: The wires used for HF-TENS and P-TENS stimulation.....	151



Figure 8.5: Summary of data analysis plan .....	154
Figure 8.6: CONSORT diagram displaying the progression of participants through the study. .....	155
Figure 8.7: Mean time taken to report pain threshold at baseline and with intervention in both groups. Change from baseline with intervention was significant for both groups. Error bars represent 95% confidence intervals. ....	158
Figure 8.8: Mean time taken to report pain tolerance at baseline and with intervention in both groups. Change from baseline with intervention was significant for both groups. However, change with HF-TENS was greater than that with P-TENS. Error bars represent 95% confidence intervals. ....	158
Figure 8.9: Mean pain endurance at baseline and with intervention in both groups. Change from baseline with intervention was significant for both groups. However, change with HF-TENS was greater than that with P-TENS. Error bars represent 95% confidence intervals. ....	159
Figure 8.10: Mean 21-NRS scores during baseline mSETT with no intervention. There were no differences between the groups at any time point. ....	161
Figure 8.11: Mean 21-NRS scores during intervention mSETT in A) the HF-TENS and B) the P-TENS groups. No significant changes from baseline were observed at any point in the P-TENS group. Mean 21-NRS scores were significantly lower than baseline from minute 6 to 10 in the HF-TENS group. ....	162
Figure 8.12: Mean individual change in 21-NRS scores throughout the mSETT in both groups. Change with HF-TENS was greater than with P-TENS in the 4 <sup>th</sup> minute and then from the 6 <sup>th</sup> to the 9 <sup>th</sup> minute. Significant differences between groups indicated by * $p < 0.05$ ; ** $p < 0.01$ , one-way ANOVA. ....	163
Figure 8.13: Mean TPRI scores at baseline and with intervention in both groups. Change from baseline with intervention was significant for both groups. No differences were found between the groups (two-way repeated measures ANOVA). Error bars represent 95% confidence intervals. ....	165
Figure 8.14: Mean SPRI scores at baseline and with intervention in both groups. Change from baseline with intervention was significant for both groups. No differences were found between the groups (two-way repeated measures ANOVA). Error bars represent 95% confidence intervals. ....	166
Figure 8.15: Mean RPRI scores at baseline and with intervention in both groups. Change from baseline with intervention was significant for both groups. No differences were found between the groups (two-way repeated measures ANOVA). Error bars represent 95% confidence intervals. ....	166
Figure 9.1: Order of intervention for each group. ....	173
Figure 9.2: A flow diagram illustrating the relationship between the normal patient journey and that of the current study. The normal clinical journey of a patient with PAD and IC at the centre where the study participants were recruited is shown on the left. In grey, the current study journey. ....	174
Figure 9.3: First testing session procedure .....	176
Figure 9.4: Second testing session procedure .....	176
Figure 9.5: Summary of data analysis plan .....	183
Figure 9.6: CONSORT diagram displaying the progression of participants through the study. .....	184

Figure 9.7: Graphs of A) ICD, B) FCD and C) ACD with placebo and intervention for both groups. Significant differences were found for ICD, FCD and ACD with HF-TENS ( $p = .004$ , $.025$ and $.025$ respectively). For LF-TENS, only difference observed was in ACD ( $p = .043$ ).....	188
Figure 9.8: Boxplots representing change in walking measures with intervention in both groups. Error bars = IQR. The only significant difference between the groups was for change in ICD. ....	189
Figure 9.9: Boxplots representing percentage change in walking measures with intervention in both groups. Error bars = IQR. The only significant difference between the groups was for percentage change in ICD. ....	189
Figure 9.10: Median ICD, FCD and ACD for all participants with Placebo and Active TENS. Statistics: Wilcoxon Signed Ranks tests. Error bars = 95% CI. ....	190
Figure 9.11: Summary of analysis and main outcomes .....	195
Figure 10.1: Graph of percentage utilisation of MPQ subclasses in Clinical and Laboratory participants. ....	222
Figure 10.2: Graph of the difference in mean PRI (R) scores between the groups for all subclasses. Positive scores indicate subclasses where the mean PRI(R) scores were greater in participants experiencing experimental ischaemic pain. ....	226
Figure 11.1: Study procedure .....	242
Figure 11.2: The focus group Topic Guide employed within this study. ....	245
Figure 12.1: Flow diagram summary of the literature review and the research questions developed from this review.....	287

## LIST OF TABLES:

Table 2.1: Current medical management of PAD risk factors. ....	41
Table 3.1: 20 Subgroups of the MPQ and the ranked pain descriptors (Melzack 1975).....	61
Table 3.2: MPQ adjectives chosen by more than 33% of participants for menstrual, arthritic, labour, dental, back and cancer pain (adapted from Dubuisson and Melzack 1976).65	
Table 4.1: Overview of recent reviews of the clinical efficacy of TENS.....	81
Table 5.1: Published studies that employed the SETT procedure to induce ischaemic pain (continued on next 4 pages) .....	91
Table 5.2: Summary of variations in SETT methods employed in published studies .....	96
Table 5.3: Details of the search strategy employed in this systematic review. ....	99
Table 5.4: Full-text articles screened and reasons if excluded from final review .....	102
Table 5.5: Articles included in the review and scores for methodological quality related to the modified Jadad scale (Appendix 3).....	102
Table 5.6: Overview of TENS parameters employed in the review .....	114
Table 5.7: Overview of the findings of the studies included in the review .....	116
Table 5.8: Summary of pilot studies investigating lower limb ischaemic pain.....	119
Table 7.1: Individual participant data for change in each measure with the mSETT.....	140
Table 7.2: ICC estimates for time to pain threshold, tolerance and endurance (measured in seconds).....	140
Table 8.1: Mean (SE) baseline data for all participants. <i>p</i> value represents result of independent student's t-test (two-tailed).....	156
Table 8.2: Mean (SE) time (secs) to pain threshold, pain tolerance and pain endurance for both groups with TENS and with no intervention (baseline) .....	156
Table 8.3: Mean (SE) PRI scores for both groups with placebo and with TENS intervention. ....	164
Table 9.1: Demographic and baseline data for all participants included in the study. The <i>p</i> values stated relate to independent student's t-tests (two tailed) of the group values. ....	185
Table 9.2: Median (IQR) ICD, FCD and ACD (in metres) and PRI scores for both groups with placebo and with TENS intervention. * = significant change within group. ....	186
Table 9.3: Median (IQR) change and percentage change in ICD, FCD, ACD and PRI scores for HF and LF-TENS groups. * = significant change between groups.....	187
Table 9.4: Spearman's Correlation Coefficients between baseline measures in all participants .....	192
Table 9.5: Spearman's Correlation Coefficients between descriptive and experimental measures.....	192
Table 9.6: Multiple regression analysis for ACD. ....	194
Table 9.7: Multiple regression analysis for $\Delta$ ACD.....	194
Table 10.1: Participants included in the analysis with clinical or induced ischaemic pain. ..	220
Table 10.2: Mean (SE) NWC in each group. ....	220
Table 10.3: Classification of subclasses and ranked adjectives included in the MPQ. Subclasses highlighted by shading and an * are those with more than 50% utilisation by the clinical group.....	223
Table 10.4: Mode adjective chosen in subclasses with more than 50% utilisation in both groups. Classification of subclasses is also included. Note the higher rank of word	

chosen in the laboratory group for categories 1, 9, 11 and 16 (highlighted in <b>bold</b> ).	224
Table 10.5: Mean (SE) PRI scores for both groups. Statistics represent independent student's t-tests (two tailed).	225
Table 10.6: Summary of the current descriptions of ischaemic pain in the literature compared with the results from the current study. Reported here are the highest ranked descriptors from the SF-MPQ (Rüger et al 2008) and the most commonly utilised adjectives from the MPQ (Current Study).	229
Table 10.7: Summary of the results from the two different methods of analysis.	231
Table 11.1: Participant demographic data at baseline. Coloured shading represents comparison between participants with darker shades of green indicating 'favourable' properties.	251
Table 11.2: Participant data at baseline and follow-up (post TENS). Coloured shading represents comparison between participants as well as pre and post TENS.	251
Table 11.3: Summary of interpretation of patients' experiences of living with PAD and IC and using TENS for daily life in patients with PAD and IC	254
Table 11.4: Summary of main themes identified in studies on the experience of living with PAD and IC	275

## ABBREVIATIONS:

---

To allow more seamless reading of the thesis, some fundamental terms have been abbreviated. Below is a comprehensive list of these abbreviations in alphabetical order along with explanation of their meaning for reference.

Abbreviation:	Meaning:
21-NRS	21 point Numerical Rating Scale
ACD	Absolute Claudication Distance
B-TENS	Burst Transcutaneous Electrical Nerve Stimulation
BMI	Body Mass Index
BP	Blood Pressure
BP (sys)	Systolic Blood Pressure
End mA	TENS Intensity at the end of the test
FCD	Functional Claudication Distance
FPQ	Fear of Pain Questionnaire
HF-TENS	High Frequency Transcutaneous Electrical Nerve Stimulation
HI	High Intensity
HR	Heart Rate
IC	Intermittent Claudication
ICC	Intraclass Correlation Coefficient
ICD	Initial Claudication Distance
IPAQ	International Physical Activity Questionnaire
LF-TENS	Low Frequency Transcutaneous Electrical Nerve Stimulation
LI	Low Intensity
MMSE	Mini Mental State Examination
MPQ	McGill Pain Questionnaire
mSETT	Modified Submaximal Effort Tourniquet Test
MSK	Musculoskeletal
MSQ	Mental Status Questionnaire
MWD	Maximal Walking Distance
NRS	Numerical Rating Scale
P-TENS	Placebo Transcutaneous Electrical Nerve Stimulation
PAD	Peripheral Arterial Disease
PCS	Pain Catastrophising Scale
PFWD	Pain Free Walking Distance
PGIC	Patient Global Impression of Change Scale
PRI	Pain Rating Index
PSEQ	Pain Self-Efficacy Questionnaire
QoL	Quality of Life
RCT	Randomised Controlled Trial
RPRI	Reactive Pain Rating Index
SETT	Submaximal Effort Tourniquet Test

<b>Abbreviation:</b>	<b>Meaning:</b>
SF-MPQ-2	Short Form McGill Pain Questionnaire 2
SpO <sub>2</sub>	Saturations of Oxygen
SPRI	Sensory Pain Rating Index
Start mA	TENS Intensity at the start of the test
TENS	Transcutaneous Electrical Nerve Stimulation
TSK	Tampa Scale of Kinesiophobia
VAS	Visual Analogue Scale
VASCUQoL	Vascular Quality of Life Questionnaire
WIQ	Walking Impairment Questionnaire
$\Delta$ ACD	Change in Absolute Claudication Distance
$\Delta$ FCD	Change in Functional Claudication Distance
$\Delta$ ICD	Change in Initial Claudication Distance
$\Delta$ mA	Change in TENS Intensity (measured in milliamps (mA))

## CHAPTER 1: INTRODUCTION

---

### 1.1: AIM OF CHAPTER 1:

---

The aim of Chapter 1 is to summarise the components that informed the development of the current project. The research questions, aims of the thesis and the outline of how each component of the research programme achieves these aims will be identified.

### 1.2: INTRODUCTION TO THE THESIS:

---

Peripheral arterial disease (PAD) is a common manifestation of systemic atherosclerosis. The cardinal symptom of PAD is intermittent claudication (IC), generally described as pain, fatigue and cramping in the lower limb(s) on exertion. PAD and especially IC causes significant disability, decreased physical function and a decrease in overall quality of life. Exercise therapy is at the core of the management of PAD and helps to reduce the chance of the disease progressing and patients suffering heart attack or stroke. Adherence to regular exercise is a problem for patients with IC. The most commonly reported symptom of IC is pain and pain is also the factor that, according to patients, limits their activity and participation (Wann-Hansson et al 2008). Current management of IC is mainly pharmaceutical and focussed on increasing perfusion in the lower limbs and slowing the progression of the disease.

This management is successful at increasing walking distance although it does not address the experience of pain. A cheap, non-pharmacological hypoalgesic intervention may be a useful adjunctive treatment that could help reduce the experience of pain. If successful this treatment could augment the efficacy of the current management of IC, lead to greater adherence to exercise therapy and ultimately help reduce the chance of progression to more serious manifestations of cardiovascular disease.

To effectively address the pain associated with IC and test possible novel interventions an in-depth understanding of the subjective quality of the pain experience is required. Currently, there is a dearth of literature investigating the pain experience and none regarding the efficacy of hypoalgesic interventions for IC pain. This study aims to address

these two aspects, exploring the pain experience of IC and investigating the effects of a common, non-pharmacological intervention on measures of pain and walking distance.

---

#### 1.2.1: The Clinical Problem:

---

There are an estimated 27 million people in North America and Europe living with PAD (Belch et al 2003; Hankey et al 2006). IC is a painful condition defined as pain usually in the calf of one or both legs, which occurs on walking, and is relieved by rest (Stewart et al 2002; Bendermacher et al 2006; Meru et al 2006).

IC is commonly but not exclusively the result of the atherosclerotic and arteriosclerotic process where the arteries become narrower and harder leading to inadequate blood supply in peripheral tissues and creation of an ischaemic environment. During exercise the decreased blood supply cannot meet the increased oxygen demand of the muscles, which then operate anaerobically. This anaerobic metabolism produces lactic acid and other metabolites that act on nerve endings causing pain (Meru et al 2006).

Patients experiencing the pain of IC are characterised by reduced levels of daily physical activity, which is associated with diminished performance of personal, social and occupational activities of daily life. Many individuals become housebound or dependent on others (Falcone et al 2003; Aquarius et al 2006). A significant problem is that up to 45% of patients do not comply with medical advice to take regular exercise and to walk 'through' IC pain (Leng et al 2000; Roche et al 2005). The reasons for this non-compliance are commonly stated as too painful, lack of supervision or definite advice, and unsatisfying results (Bartelink et al 2004; Kruidenier et al 2009c). Since both of these activities relieve IC and help minimise further deterioration, for example into chronic heart disease and stroke (Izquierdo-Porrera et al 2000; Wannamathee and Shaper 2001), the lack of detailed understanding of IC and its effects on general exercise and function is a major problem.

IC represents a chronic pain problem. Chronic pain can be defined as daily pain reoccurring for more than 6 months, usually beyond the time for normal organic healing and is associated with negative psychosocial effects (Vlaeyen et al 1995; Crombez et al 1999).



Clinicians are acutely aware of the link between the chronic nature of IC and deterioration in function and quality of life in patients with PAD (Falcone et al 2003). Nevertheless, unlike other major chronic pain syndromes such as cancer pain, arthritis and post-surgical pain (Graham et al 1980; Roche and Heim 1997; Roche et al 2003; Bruce et al 2004; Ngamkham et al 2012), the subjective nature of IC (i.e. the disease-specific quality and intensity of the pain), has not been explored.

---

### 1.2.2: Subjective Description of IC Pain:

---

In recent decades pain researchers have shown the value of obtaining patients' subjective descriptions of chronic pain syndromes by using the multidimensional McGill Pain Questionnaire (MPQ) (Melzack 1975). The MPQ details the subjective description of pain in sensory-discriminative, affective-motivational and cognitive-evaluative dimensions, which reflect the complexity of pain perception in the brain (Treede et al 1999; Mayer et al 2005). These dimensions are assessed via 78 pain adjectives separated into 20 subclasses and ranked within these subclasses in order of intensity. Despite its descriptive, subjective nature the MPQ can also produce a single quantitative score of pain intensity, termed the Pain Rating Index (PRI). The MPQ has now become a frequently used tool in the assessment, diagnosis and management of complex, chronic pain syndromes (Melzack 1987; Wright et al 2001) but has not been used to describe IC pain in suitably large populations.

One pilot study used the MPQ retrospectively to investigate IC pain during walking (Roche et al 2005). High PRI scores were reported along with participants' high percentage use of specific sensory and affective-evaluative descriptors from the MPQ (Roche et al 2005). The conclusions were limited however due to the small sample size and retrospective nature of the study. Further study examining IC pain when present and in a larger sample are required to validate these descriptions of IC pain and serve as a clinical profile of IC. This initial indication, that IC pain is severe in intensity, enforces the importance of having a more multidimensional investigation into IC and the importance of testing and effectively relieving this pain.

---

### 1.2.3: Current Management of IC:

---

Current treatment of IC pain is mainly pharmaceutical and aims to delay the onset of pain by altering physiological factors in the limbs such as reducing blood viscosity and increasing vessel diameter thus delaying the creation of the ischaemic environment. Although this type of treatment can be successful pharmaceutical interventions are expensive, potentially problematic in relation to accurate dosing and can cause side effects. In addition, to gain the full benefits from exercise therapy the person needs to walk 'through' pain, (i.e. endure the ischaemic environment in their limb(s)). This helps to encourage the formation of collateral vessels and improve muscular and walking efficiency (Laurenzano et al 2009; Beckitt et al 2012). As pharmaceutical treatment delays the onset of pain, rather than affecting the pain itself, patients are less likely to walk 'through' an ischaemic environment and gain the full benefit of exercise therapy.

---

### 1.2.4: Possible Adjunct to Current Treatment of IC:

---

Transcutaneous Electrical Nerve Stimulation (TENS) is acknowledged as a safe, portable and inexpensive method of providing non-invasive pain relief (Johnson 2001; Vance et al 2012). TENS is a form of mild electrical stimulation and has consistently shown greater analgesic effects than placebo TENS, chiefly in musculoskeletal pain problems (Law and Cheing 2004) but also in postoperative (Hamza et al 1999) and neuropathic pain (Somers and Somers 1999). It is a non-invasive modality packaged in a small, portable unit that is easy to apply via small electrodes placed on the skin. It can be kept in a pocket or clipped to a trouser belt and is used widely and daily by patients with chronic pain to reduce their pain, improve their daily functioning and in some cases return to work (Johnson et al 1991; Sluka and Walsh 2003). However, it is not known to what extent TENS (and more specifically the different stimulation patterns of TENS that can be applied) may modify the barriers mentioned above in patients with PAD. Studies conducted to date suggest that the fast-acting, reflexive mechanism of High Frequency TENS (HF-TENS) may act most effectively at the mild (pain threshold) level of the pain experience. Low Frequency TENS (LF-TENS) however may act most effectively at the stronger (pain tolerance) level of the pain experience due to extrasegmental but longer-lasting analgesic effects (Barlas and Lundberg 2006).

Possibly due to the focus on medical management and the limited investigation of IC pain, TENS has not been tested as an effective method of pain relief of IC. Also the potential for High Frequency (HF) versus Low Frequency (LF) patterns of TENS to affect different portions of the IC pain experience has not been examined. The potential for HF/LF-TENS to modify IC pain when it is mild (which normally occurs in PAD patients after walking a short distance), while it builds up (during continued walking), and when it becomes intolerable, is the basis for this proposal to test these two types of TENS stimulus pattern on IC.

---

#### 1.2.5: Laboratory Investigations of Pain:

---

Clinical pain syndromes are complex in nature with both sensory-discriminative and affective-evaluative components occurring simultaneously (Woolf 1979). These factors make patients with clinical pain syndromes less than ideal subjects for initial investigations into the efficacy of potential analgesics (Staahl and Drewes 2004). Clinically, patients often have confounding co-morbidities and are likely to be taking some form of medication (Staahl and Drewes 2004). Patients may also interpret other effects of the intervention as a relief of pain. For example, a reduction in disease-related anxiety or depression may be misinterpreted as a reduction in pain.

Experimental pain models are advantageous in pre-clinical investigation of an intervention as they allow some quantitative control over the input that subjects receive (Woolf 1979). The investigator can control the experimentally induced pain, i.e. the location, nature, intensity, frequency and duration and provide quantitative measures of the psychophysical, behavioural or neurophysiological responses (Graven-Nielsen et al 2001; Staahl and Drewes 2004). Therefore prior to examining the effects of TENS on clinical IC pain it would be advantageous to examine its efficacy on an experimental model of ischaemic pain.

---

#### 1.2.6: Laboratory Ischaemic Pain:

---

The Submaximal Effort Tourniquet Test (SETT) is an experimental method of inducing ischaemic pain in the upper limb of healthy volunteers. The effects of TENS have been investigated on experimental ischaemic pain in the upper limb (Woolf 1979; Roche et al 1984; Walsh et al 1995a; Chen and Johnson 2011). TENS has been shown to significantly

increase time taken to report pain threshold, time taken to report pain tolerance and overall pain endurance in the upper limb (Woolf 1979; Roche et al 1984; Chen and Johnson 2011).

IC pain however occurs in the lower limb and when standing. Despite these promising results of TENS in the upper limb it is not known whether TENS will produce the same results in the lower limb.

Establishing a valid and reliable method of inducing lower limb ischaemic pain could be useful. If developed this method could be used for investigation of the qualities of ischaemic pain. In addition, it could provide a platform to investigate how those qualities of pain respond to interventions. It is anticipated, for example, that laboratory-induced ischaemic pain may have similar sensory-discriminative qualities to IC but have fewer affective-motivational and cognitive-evaluative components. Such a non-chronic profile of the sensory-discriminative components of ischaemic pain could be a useful way to examine how TENS affects the common sensory experience of IC pain.

A series of pilot studies have adapted the upper limb SETT to the lower limb and applied it in both supine and/or standing postures with laboratory participants (Roche et al 2007). These studies have developed a method for inducing ischaemic pain in the lower limb of healthy volunteers in standing. This modified SETT (mSETT) has also been used to test the effects of TENS on lower limb ischaemic pain with analgesic trends observed. However, these did not reach significance because of limitations in sample sizes and study methodologies (Roche et al 2007). Further investigation of the effects of TENS on lower limb experimental ischaemic pain is required prior to examining its effects in patients with IC.

---

#### 1.2.7: Summary:

---

In summary, the clinical problem of IC is well established. An aspect that has so far been neglected is the pain experience of IC. The recording and evaluation of the subjective descriptions of IC pain could be an effective means of improving the understanding and management of patients with IC. The MPQ provides a method by which the subjective descriptions of IC pain could be recorded.

Although never tested for IC pain, TENS is a possible useful intervention. Due to the complex, chronic nature of clinical IC pain, an investigation of the effects of TENS on lower limb experimental ischaemic pain is warranted prior to clinical investigation. This examination would allow exploration of the qualities of experimental ischaemic pain and the effect of TENS on these qualities. Any hypoalgesic effects observed in lower limb experimental ischaemic pain could be used to inform the study of TENS for IC pain in a clinical population.

### 1.3: RESEARCH QUESTIONS ADDRESSED IN THIS THESIS:

---

There are the two research questions addressed in this thesis:

- What qualities characterise the subjective description of IC pain?
- What are the effects of TENS on measures of pain and walking performance in patients with IC?

### 1.4: AIMS AND OBJECTIVES:

---

From these two questions the aims of this project are formulated. One aim is to investigate the subjective description of the multidimensional qualities of ischaemic pain. The second aim is to investigate the hypoalgesic effects of TENS on lower limb ischaemic pain and walking performance in patients with IC.

These aims can be addressed through four clear objectives that are linked to four distinct studies:

#### **Objective 1: to develop and validate the mSETT in the lower limb of healthy volunteers.**

This objective aims to establish the mSETT as a reliable method of inducing ischaemic pain in the lower limb of healthy volunteers. This will contribute to both aims of the project by establishing a method that allows investigation of the subjective descriptive qualities of lower limb ischaemic pain and examination of the effects of TENS on these qualities.

- Study 1: An examination of the test re-test reliability of the ability of the mSETT to induce consistent levels of pain was conducted (Chapter 7). A laboratory study is

proposed that examines the pain induced by the mSETT in healthy volunteers. The ability of the mSETT to induce comparable levels of pain on separate occasions will be examined in a preliminary validation study.

**Objective 2: to investigate the effects of TENS on the pain induced by the mSETT.** This objective contributes evidence regarding the effects of TENS on lower limb ischaemic pain and more specifically which aspects of the pain experience are affected by TENS intervention. Again this objective will contribute to both aims as MPQ descriptions of ischaemic pain will be recorded and the effects of TENS on lower limb ischaemic pain investigated.

- Study 2: An investigation into the hypoalgesic effects of HF-TENS on mSETT induced pain in healthy volunteers (Chapter 8). Following the validation study another laboratory study is proposed that investigates the effects of HF-TENS and Placebo TENS (P-TENS) on reports of mSETT-induced pain intensity and quality as measured by the MPQ.

**Objective 3: to investigate the effects of TENS on pain and walking performance in patients with IC.** This objective is central to the attempt of this thesis to address the identified clinical problem of IC. Both aims will be addressed by investigating the effects of TENS on IC pain and walking performance and recording of the descriptions of clinical ischaemic pain with the MPQ.

- Study 3: An investigation into the hypoalgesic effects of HF and LF-TENS on measures of pain and walking performance in patients with IC (Chapter 9). A clinical Medical Research Council (MRC) phase IIa, ‘proof of concept’ study is proposed that investigates the effects of TENS on walking performance in patients with PAD and IC. This study will also examine the psychosocial aspects of IC pain and relationships to walking performance.

**Objective 4: to record and compare the subjective descriptions of the pain experience associated with IC and mSETT induced pain.** This objective will specifically address the first aim of the project: to investigate the subjective description of ischaemic pain. By comparing

descriptions of pain between the clinical IC population and healthy volunteers experiencing the mSETT, the subjective descriptions of lower limb ischaemic pain can be explored.

- Study 4: A post hoc examination of the pain descriptions as recorded by the MPQ in patients with IC and healthy volunteers experiencing mSETT induced pain (Chapter 10). The specific subjective nature and quality of IC pain will be compared to that induced by the mSETT.

The original contribution of this project is threefold. The preliminary validation of the mSETT procedure is unique as a method of inducing ischaemic pain in the lower limb of healthy volunteers. The detailed, subjective description of lower limb ischaemic pain in the laboratory and clinical settings is also unique and the investigation of TENS as an adjunctive intervention for IC pain is novel. The findings of this project could be used to make recommendations for future management of lower limb ischaemic pain and the evaluation of TENS as an adjunctive treatment for PAD and IC.

### 1.5: STRUCTURE OF THESIS:

---

The flow diagram in Figure 1.1 details the structure of this thesis and the progress and interaction of the research programme presented in this thesis. The general contents of each chapter are also highlighted.

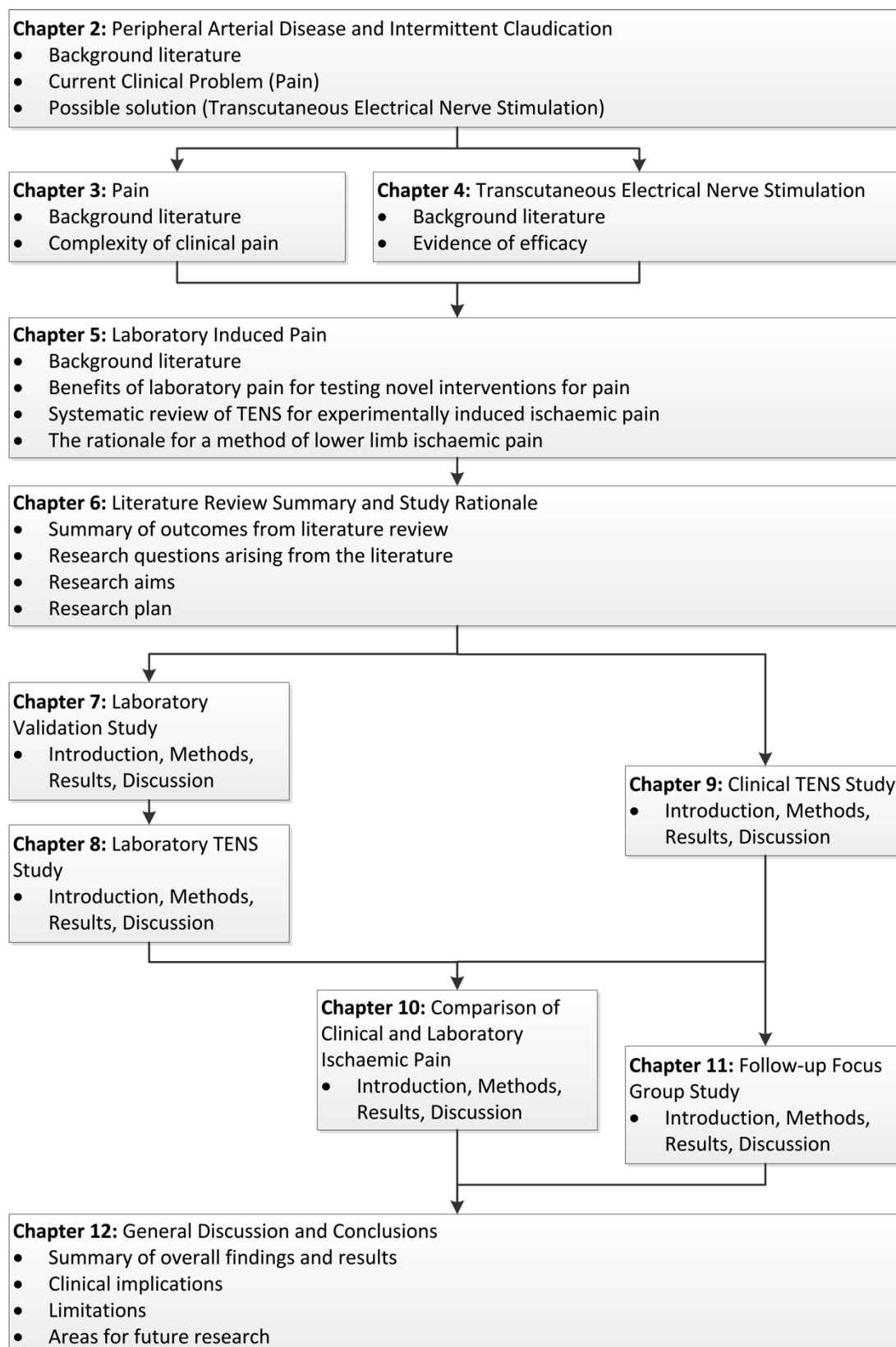


Figure 1.1: Flow diagram of thesis structure. The additional study not discussed in section 1.4 above will be introduced and discussed in Chapter 11. This is due to its nature as a follow-up study rather than a part of the initial project plan.



## 1.6: SUMMARY OF THESIS CONTENT:

---

### 1.6.1: Chapter 2: Peripheral Arterial Disease (PAD) and Intermittent Claudication (IC)

---

This chapter provides the background to PAD and IC and summarises what is known about the disease. Special focus will be afforded to the experience of IC and its impact on function, QoL, psychosocial health and the role of pain as being central to the disease process and responsible for many of the functional limitations associated with IC. The current management of IC pain will be discussed in this chapter. The advantages and disadvantages of the current approaches will be explored along with possible options for future management of IC.

### 1.6.2: Chapter 3: Pain

---

The aim of this chapter is to provide a summary of the current understanding of pain and relate this to the study of IC. The basic definitions and concepts will be discussed followed by a more in-depth exploration of the measurement and description of pain and the associated psychosocial factors. Finally IC pain will be discussed in this context.

### 1.6.3: Chapter 4: Transcutaneous Electrical Nerve Stimulation (TENS)

---

This chapter will briefly explore possible non-invasive, adjunctive methods of pain management in IC. It will justify the use of Transcutaneous Electrical Nerve Stimulation (TENS) as the selected option, examine its mechanisms of action and discuss the evidence for its pain-relieving effects.

### 1.6.4: Chapter 5: Laboratory-Induced Pain

---

This chapter will explore issues in pain research. The benefits of experimental pain models will be discussed with a focus on laboratory-induced ischaemic pain. The reported effects of TENS on this laboratory-induced ischaemic pain will be examined along with the rationale for development of a laboratory-induced ischaemic pain method in the lower limb of a standing subject.

---

#### 1.6.5: Chapter 6: Literature Review Summary and Rationale

---

This chapter will summarise the aims of this thesis as informed by the literature review and outline how each component of the research programme plans to address these aims.

---

#### 1.6.6: Chapter 7: Experiment One - Test-Retest Reliability of the modified SETT

---

A pilot study conducted to examine the test-retest reliability of the mSETT will be described in this chapter. The results observed and contribution to the thesis will be explored.

---

#### 1.6.7: Chapter 8: Experiment Two - The Effects of TENS on mSETT-Induced Pain

---

The aim of this chapter is to describe the investigation of mSETT-induced, lower limb ischaemic pain and the effects of HF-TENS on measures of pain compared to P-TENS.

---

#### 1.6.8: Chapter 9: Experiment Three - The Effects of TENS on Pain and Walking Performance in Patients with PAD and IC

---

The aim of chapter nine is to describe the investigation of the effects of TENS on pain and walking performance in patients with PAD and IC. The effects of HF- and LF-TENS were investigated using a standardised treadmill test. Measures of pain and walking performance were used to examine the effects of TENS compared to P-TENS.

---

#### 1.6.9: Chapter 10: Comparison of Experimental and Clinical Ischaemic Pain

---

An analysis of MPQ descriptions of experimentally induced and clinical ischaemic pain will be presented in this chapter. The similarities and differences in subjective descriptions of pain will be discussed.

---

#### 1.6.10: Chapter 11: A Pilot Investigation into Patients' Experiences of Using TENS for Daily Life with PAD and IC

---

Chapter eleven describes a preliminary follow-up study of a small selection of patients with PAD and IC. This qualitative study was conducted as a preliminary investigation of the experience of using TENS at home for daily life with PAD and IC. This additional study was conceived in response to research questions raised by the results from the clinical study.

---

#### 1.6.11: Chapter 12: General Discussions and Conclusions

---

The findings of the research programme will be discussed in relation to the research questions and aims. Conclusions regarding the results of the studies will be discussed based on the data presented. The clinical implications, limitations and recommendations of this research programme will also be presented.

## CHAPTER 2: PERIPHERAL ARTERIAL DISEASE (PAD) AND INTERMITTENT CLAUDICATION (IC)

---

### 2.1: AIM OF CHAPTER 2:

---

The aim of this chapter is to outline the clinical problem of Peripheral Arterial Disease (PAD) and Intermittent Claudication (IC). The aetiology, epidemiology, prognosis and current management of PAD and IC will be discussed, highlighting the current state of the published literature surrounding the topic (see sections 2.2 and 2.3). Special attention will be paid to the perceived gaps in understanding and limitations in management of IC (section 2.4). The relationships between these factors and the aims of the thesis will be explored indicating the possible contributions of the current project to the clinical evidence base.

### 2.2: PERIPHERAL ARTERIAL DISEASE:

---

Peripheral Arterial Disease (PAD) has been described as:

*“a diverse group of disorders that lead to progressive stenosis or occlusion, or aneurysmal dilation, of the aorta and its non-coronary branch arteries, including the carotid, upper extremity, visceral, and lower extremity arterial branches. Peripheral arterial disease is the preferred clinical term that should be used to denote stenotic, occlusive, and aneurysmal diseases of the aorta and its branch arteries, exclusive of the coronary arteries”*

(Hirsch et al 2005, p466)

PAD is operationally defined as an obstruction of blood flow into an arterial tree excluding the intracranial or coronary circulations and is most commonly a result of the atherosclerotic process in multiple vascular beds (Garcia 2006; Hankey et al 2006; Gornik and Creager 2006; Norgren et al 2007). The reported disease prevalence of PAD ranges from 3-30% (Criqui et al 1985; Hiatt et al 1995; Hirsch et al 2001; Murabito et al 2002; Belch et al 2003; Selvin and Erlinger 2004; Olin et al 2010) and there are approximately 2.7 million people in the UK and 27 million people in North America and Europe living with PAD (Belch et al 2003; Hankey et al 2006).

The most common cause of death in patients with PAD is Coronary Artery Disease (CAD) (40-60% of deaths) (Norgren et al 2007). Additionally, Cerebral Vascular Disease (CVD)

accounts for 10-20% of deaths and other vascular events, approximately 10%. Only 20-30% of patients with PAD die of non-cardiovascular causes (Norgren et al 2007).

Myocardial Infarction (MI) and Cerebrovascular Accident (CVA) are the main contributors to the high mortality rate, alone contributing to approximately 25-30% of all mortality in the PAD population within 5 years of diagnosis (Gornik and Creager 2006; Hankey et al 2006; Norgren et al 2007).

PAD is a clinical manifestation of cardiovascular disease. PAD has an age, and sex-adjusted risk ratio of 3.34 for all cause mortality (Garcia 2006; Heald et al 2006; Roger et al 2011). Cardiovascular disease affects approximately 80 million people in the USA and 2.5 million in the UK (BHF 2008; Roger et al 2011). It is the most common cause of mortality, responsible for approximately 200,000 deaths in the UK each year and an annual healthcare cost of 14.4 billion pounds (BHF 2008). In the USA, the annual figure is estimated to be 503.2 billion dollars in direct and indirect costs (Olin et al 2010).

### 2.3: INTERMITTENT CLAUDICATION

---

PAD is mostly asymptomatic in the early stages although as the disease progresses, the continuing atherogenesis may manifest as Intermittent Claudication (IC) (Garcia 2006; Olin et al 2010). IC is the cardinal symptom of PAD and is frequently, operationally defined as pain in the lower limb(s) that manifests during walking, and is relieved by rest (Stewart et al 2002; Bendermacher et al 2006). The prevalence of IC has been reported as 3% in people aged 40 years, rising to 6% in those aged 60 years (Norgren et al 2007). Approximately 60% of patients with PAD report leg symptoms with 30% reporting typical IC (Murabito et al 2002; Olin et al 2010).

IC describes the collection of symptoms that occurs whilst walking and is the result of decreased perfusion in the periphery (Olin et al 2010). These symptoms can include pain, muscle cramps, muscle weakness, paraesthesia and altered gait pattern. This collection of symptoms can be relatively stable over time although they are associated with significant levels of functional disability, psychological distress and increased risk of morbidity and

mortality independent of PAD (Treat-Jacobson et al 2002; Falcone et al 2003; Olin et al 2010). 'IC pain' refers specifically to the pain experienced during IC (Rüger et al 2008).

---

#### 2.3.1: IC Pain:

---

The mechanisms associated with IC pain are not fully understood (Graven-Nielsen and Arendt-Nielsen 2008; Gardner et al 2010). It is accepted that IC pain is a result of tissue ischaemia but how this leads to the perception of pain is still debated. Previous authors have proposed that ischaemic pain is a result of the following different mechanisms: a build up of a chemical mechanism, termed 'Factor P' (Lewis 1932); a build up of lactate in the muscle tissues (Saltin et al 1981); an increased concentration of potassium (Harpuder and Stein 1943); general tissue acidosis (Allsop et al 1990) and an increased concentration of interstitial adenosine (Costa et al 1999). None of these theories have been conclusively demonstrated and the most recent research suggests that pain originates from the vascular system with contribution from the exercising muscle (Graven-Nielsen and Arendt-Nielsen 2008).

The PAD literature commonly reports that IC pain is the result of the atherosclerotic process and arises from dual mechanisms: 'ischaemic mismatch' and peripheral neuropathy (Rieger and Scheffler 1999; Lang et al 2006). Ischaemic mismatch develops due to inadequate blood supply, and thus oxygenation, of peripheral tissues during walking (Garcia 2006; Meru et al 2006; Gardner et al 2010). During walking the muscles of the lower limb operate anaerobically owing to the limited blood supply. It is thought to be the by-products of this anaerobic metabolism (lactic acid and other metabolites) that sensitise and stimulate chemo-sensitive nociceptors (chemoreceptors), causing the perception of leg pain (Rieger and Scheffler 1999; Meru et al 2006; Graven-Nielsen and Arendt-Nielsen 2008). The neuropathic component of IC pain is thought to be a result of prolonged reduction in perfusion to the neural tissues distal to the atherosclerotic lesion (Rieger and Scheffler 1999; Lang et al 2006). This reduced perfusion of neural tissues has been shown to lead to peripheral neuropathy, axonal degeneration and central sensitisation, accentuating the perception of pain from the ischaemic tissue (Lang et al 2006).

Clinicians are acutely aware of the link between IC and deterioration in function and quality of life in patients with PAD (Falcone et al 2003). Nevertheless, unlike other major chronic pain syndromes such as cancer pain and arthritis (Roche and Heim 1997; Roche et al 2003), the subjective nature of IC (i.e. the disease-specific quality and intensity of the pain), has not been fully explored.

Rüger et al (2008) used the Short Form of the MPQ (SF-MPQ) (Melzack 1987) to assess pain in patients with PAD and IC. They recruited 102 participants with confirmed diagnosis of PAD and IC pain during exercise or at rest. A VAS and the SF-MPQ were used to measure the multidimensional nature of the pain. Of the participants, 61 had IC (pain on exertion) and 41 had Critical Limb Ischaemia (CLI) (further progressed disease characterised by pain at rest). Intensity of IC pain was reported as  $6.8 \pm 0.3$  (VAS 0-10; mean  $\pm$  SD) and mean Total Pain Rating Index (TPRI) score was  $9.4 (\pm 0.9)$  (TPRI 0-45) demonstrating a high pain intensity as measured by the VAS but a contrastingly low TPRI score. The SF-MPQ data demonstrated a high percentage usage of specific sensory descriptors: 'stabbing', 'cramping' and 'aching'. However, the descriptor that was used by the greatest number of participants was the affective-evaluative descriptor: 'tiring-exhausting'. These findings indicate that patients with IC or CLI experience a substantial intensity of pain and this experience consists of common, specific sensory and affective components.

The main limitation of this study is due to the SF-MPQ being used rather than the full version. This could explain the lower TPRI scores as the SF-MPQ excludes adjectives that might best describe IC pain (tugging/ wrenching (Sensory); wretched/ blinding (Affective) and annoying/ unbearable (Evaluative)).

Another limitation to this study is that it is retrospective and relied on the participants' ability to accurately recall and rate the pain they experience. This could have resulted in inaccuracies in the pain descriptions reported with some aspects being exaggerated and others diminished.

One pilot study used the full MPQ to investigate IC pain during walking (Roche et al 2005). Thirty-one participants were recruited who had PAD and IC. A Visual Analogue Scale (VAS) and the MPQ were used to measure IC pain retrospectively. The mean VAS ( $\pm$ SD) was 5.31 ( $\pm$ 1.64) and PRI score was 25.29 ( $\pm$ 10.42) demonstrating a high intensity of pain. High percentage use of specific sensory and affective-evaluative descriptors from the MPQ was also reported (Roche et al 2005). The conclusions regarding the nature of IC pain are limited however, due to the small sample size and retrospective nature of the study.

Further study is required that uses the full MPQ and examines IC pain immediately after exercise to validate these descriptions of the IC pain experience and serve as a qualitative profile of IC. The results from these studies of patients with IC indicate that the pain experienced is severe in intensity and unique in quality. This supports the hypothesis that the pain of IC has a significant effect on the limited walking ability and decreased quality of life in patients with PAD. If this hypothesis were true, this would also suggest a need for further investigation and testing of interventions for IC pain.

Regardless of the generating mechanisms, IC pain is experienced as severe muscle pain whilst walking and results in significant reduction in Quality of Life (QoL) (Chetter et al 1997; King et al 2012). Physiological variables such as Ankle Brachial Pressure Index (ABPI) have not been found to sufficiently predict walking tolerance or behaviour (Kruidenier et al 2009a). Psychosocial aspects such as walking intentions and perceived behavioural control however have been found to account for a large proportion of variance in walking (Galea and Bray 2007).

---

### 2.3.2: Psychosocial Aspects of IC:

---

‘Psychosocial’ can be defined as ‘relating to the interrelation of social factors and individual thought and behaviour’ (Oxford Dictionaries 2010). The psychosocial aspects of a condition refer to those additional to the measurable physiological status of a person’s condition, they are the associated psychological and social factors, regardless of direction of relationship e.g. somatic distress, pain amplification, depression, fear, anxiety, catastrophising (Carragee et al 2005).



Patients experiencing IC are characterised by reduced levels of daily physical activity, which is associated with diminished performance of personal, social and occupational activities of daily life and many individuals become housebound or dependent on others (Falcone et al 2003; Aquarius et al 2006). Impaired physical functioning in patients with PAD and IC has been found to lead to an inability to continue full-time employment, feelings of social isolation and inadequacy, and believing they had become a burden to family (Treat-Jacobson et al 2002).

Despite the link between PAD and IC and decreased QoL and the inability of physiological variables to predict walking, there are a limited number of studies that examine the psychosocial nature of IC pain.

A pilot study (Roche et al 2005) examined the relationships between walking and cognitive-behavioural factors in patients with PAD and IC. Statistically significant correlations were reported between Perceived Disability (Roland Disability Questionnaire) and cognitive-behavioural measures including: pain self-efficacy; fear of pain/re-injury; frustration; helplessness; pain intensity (Visual Analogue Scale) and quality (MPQ). This study, although limited in sample size (n=31), indicated the uniqueness in quality and severity of IC pain. It also found significant relationships between the associated psychosocial factors measured and functional performance (Roche et al 2005).

Smolderen et al (2008) examined depressive symptoms in patients with PAD. Participants with PAD and IC (n=166) were recruited from a vascular outpatient clinic and followed up at 6, 12 and 18 months. Participants' baseline characteristics, resting Ankle Brachial Pressure Index (ABPI) (measure of lower limb arterial stenosis), Pain-Free Walking Distance (PFWD) and Maximal Walking Distance (MWD) on a standardised treadmill test were recorded at baseline along with their score on the Center for Epidemiological Studies Depression Scale (CES-D). At each time point after baseline, the CES-D was completed but no other measures were repeated. At baseline, 16% of participants were classified as having 'depressive symptoms'. This group of participants were found to have significantly decreased PFWD and

MWD compared to the rest of the sample (Smolderen et al 2008). At each follow-up time point these levels of depression remained constant and they were found to be related to other aspects of the disease including: having no partner, smoking, hyperlipidaemia, hypertension, decreased walking distance, increased intake of psychotropic medication and report of back symptoms (Smolderen et al 2008). The analysis only indicated likelihood odds rather than any direct causal relationships. However, the significant and complex associations are suggestive of a complex, chronic disease process with significant psychosocial aspects. The strengths of this study include a large sample size that consisted exclusively of patients with IC and there was no drop out ensuring that the results are a true representation of the sample. However, the measure of depression used (CES-D) is a somewhat blunt instrument although useful in this design when the aim was to classify participants into groups dependent on their depressive symptoms. A more detailed questionnaire, set of questionnaires or qualitative methodology, could give more information regarding the different aspects of their depressive symptoms and possibly identify specific targets for intervention.

Garnefski et al (2009) examined depressive symptoms in more detail in a sample of 88 patients with PAD and IC. In a questionnaire-based study they examined the different coping strategies (goal re-engagement or goal disengagement) adopted by these patients in relation to depressive symptoms, catastrophising, physical limitations, age, gender and positive refocusing. Depressive symptoms were found to be associated with increased catastrophising and physical limitations and decreased goal re-engagement and positive refocusing. This suggests that focusing on the disease in a catastrophic manner is a maladaptive coping strategy and is associated with more symptoms of depression. Coping by re-engaging in alternative, meaningful goals is an adaptive strategy and associated with less depressive symptoms (Garnefski et al 2009). This study was limited due to the exclusive use of questionnaires as a method of data collection, which could be susceptible to reporter bias. Many of these variables are however hard to measure without using self-report questionnaires. Future studies could perhaps employ qualitative methods, e.g. interviews, to gain a richer understanding of the patient experience. Also, the response rate was only 60%, meaning that it may not be a true representation of the population.

These two studies demonstrate an association between psychosocial factors and PAD and IC although they are not without limitations. Both heavily relied on self-report measures to provide a general overview of the population. To comprehensively address the question of direction of relationships, further qualitative studies are required to identify the disease-specific psychosocial constructs that need to be measured and secondly, additional longitudinal studies are required to test the relationships between these constructs.

All of the studies discussed recommend further detailed and expansive investigation of the psychosocial factors of PAD and IC and emphasise the need for a detailed understanding of the pain experience (Roche et al 2005; Smolderen et al 2008; Garnefski et al 2009). IC is a chronic condition and as such is associated with psychosocial effects (Galea and Bray 2007). A detailed understanding of the IC pain experience and associated psychosocial factors could be beneficial in the development of management strategies that aim to reduce the burden of PAD and IC.

#### 2.4: MANAGEMENT OF PAD AND IC:

---

Currently there is no cure for atherosclerosis and therefore, PAD or IC. The primary recommended focus of treatment is atherosclerosis risk factor modification and management (SIGN 2006; Norgren et al 2007).

Atherosclerosis is a systemic disease, typically affecting multiple vascular beds concurrently. As such, the risk factors for PAD are similar to those of other atherosclerotic diseases, such as coronary artery disease (Smith et al 2004). Age, family history of cardiovascular disease, dyslipidaemia, smoking, diabetes mellitus, hypertension and metabolic syndrome are the main risk factors for developing atherosclerosis and thus PAD (Smith et al 2004; Garcia 2006; Norgren et al 2007). Diabetes and smoking are thought to be the strongest risk factors of PAD. Smoking is the most important modifiable risk factor, increasing the risk of developing PAD threefold (Smith et al 2004). Race (non-Hispanic black), gender (male), inflammatory markers, hyperviscosity and hypercoagulable states, hyperhomocysteinemia

and chronic renal insufficiency also have positive associations with increased risk of developing PAD (Norgren et al 2007).

Patients with PAD have multiple atherosclerosis risk factors and extensive atherosclerotic disease, which puts them at increased risk of cardiovascular events (Gornik and Creager 2006; Norgren et al 2007; Olin et al 2010). As many patients with PAD are asymptomatic (approximately 40%), they are not identified and thus their atherosclerotic risk factors are not adequately identified and managed (Hirsch et al 2005; Norgren et al 2007). As discussed, a diagnosis of PAD increases the odds of all-cause mortality, and especially cardiovascular disease mortality. Therefore, aggressive risk factor modification is indicated when diagnosed (Hirsch et al 2005; Norgren et al 2007).

There are numerous recommendations and clear guidance for atherosclerotic risk factor modification in PAD and CVD. Table 2.1 summarises the current medical management of PAD risk factors and the supporting research.

Invasive options, including endovascular and surgical management are available but are normally reserved for severe cases where there is need to salvage a threatened limb (Almahameed and Bhatt 2006). Invasive therapy may also be considered in patients with vocation or lifestyle-limiting IC pain that have shown poor response to exercise and pharmacotherapy (Almahameed and Bhatt 2006).

Exercise Therapy is recommended as a first line treatment for PAD and IC (Hirsch et al 2005). Specifically, supervised exercise training for at least 30-45 minutes, 3 times a week for a period of 12 weeks (Hirsch et al 2005; Layden et al 2012). Physical activity/exercise is also recommended for the management of cardiovascular disease as increased physical activity has been shown to help modify a number of important risk factors (De Backer et al 2003).

Table 2.1: Current medical management of PAD risk factors.

<b>Risk factor</b>	<b>Intervention</b>	<b>Method/Comment</b>	<b>Evidence for Efficacy</b>
Smoking	Smoking Cessation	Education, Advice and Counselling Nicotine replacement therapy Bupropion	Jorenby et al (1999) Anthonisen et al (2005)
Increased BMI	Weight Reduction	Counselling Diet modification Exercise Therapy	Yusuf et al (2005)
Hyperlipidaemia	Pharmacotherapy	Diet modification Statins Exercise Therapy	HPSCG (2002)
Hypertension	Pharmacotherapy	Thiazides ACE inhibitors Beta-Blockers Exercise Therapy	Yusuf et al (2000) ESH/ESC (2003)
Diabetes Mellitus	Blood Glucose Control	Diet Control Insulin-sensitising agents	Dormandy et al (2005)
Homocysteine	Avoid folate supplementation	Do Not take Folate Supplements	Bonaa et al (2006) Lonn et al (2006)
Inflammatory Markers	Pharmacotherapy	Antiplatelet Drug Therapy Aspirin Clopidogrel	CAPRIE Steering Committee (1996) Antithrombotic Trialists' Collaboration (2002)

#### 2.4.1: Exercise Therapy:

Exercise therapy interventions have been shown to have a significant positive effect on increasing self-report physical activity, measured cardio-respiratory fitness, exercise time and functional ability in patients with PAD and IC (Gardner and Poehlman 1995; Leng et al 2000; Regensteiner and Treat-Jacobson 2001; Gardner et al 2001; Stewart et al 2002; Bulmer and Coombes 2004; Hillsdon et al 2005; Carman and Fernandez 2006; Gardner and Afaq 2008). The mechanisms behind exercise therapy and the improvement in walking distance in patients with IC remains unclear (Carman and Fernandez 2006). It is thought that there are a number of contributing factors, including the following: improved collateral circulation; an improvement in rheological characteristics of the blood; increased cellular oxygen uptake from the blood; improvements in walking efficiency; improvements in

endothelial function, metabolic adaptations in skeletal muscle and improvement in psychosocial factors (Leng et al 2000; Stewart et al 2002; Carman and Fernandez 2006; Milani and Lavie 2007) (see Figure 2.2).

There are a number of studies that have investigated exercise therapy for IC patients. Of these studies there is a wide variation in results obtained. The Cochrane Review by Leng et al (2000) found that all of the included studies demonstrated significant improvements in walking distance with an average improvement of approximately 150% although the range of improvement was wide: 74-230%. Bulmer and Coombes (2004) also observed similar wide ranges of improvements in their meta-analysis. A median improvement of 83% was noted in absolute walking ability with a range of 23-210% (Bulmer and Coombes 2004). A Cochrane Review by Bendermacher et al (2006) which compared the effect of supervised versus non-supervised exercise therapy observed a 35-39% increase in maximal walking distance in eight separate trials. The broad ranges reported in these reviews are likely due to differences in the components of the exercise programmes used, such as training intensity, level of supervision, duration of the programme and heterogeneity in the study populations.

The two Cochrane Reviews concluded that the most effective course was a 6 month programme of thrice weekly supervised exercise classes lasting more than, or equal to 30 minutes, incorporating intermittent walking to near-maximal pain (Leng et al 2000; Bendermacher et al 2006). Bulmer and Coombes (2004) agree except they suggest that training to pain-free thresholds is as beneficial as training to higher intensity (i.e. to maximal pain). The authors however, provide only one study supporting this claim, and acknowledge the difficulty of systemically assessing the effect of training intensity on IC pain (Bulmer and Coombes 2004).

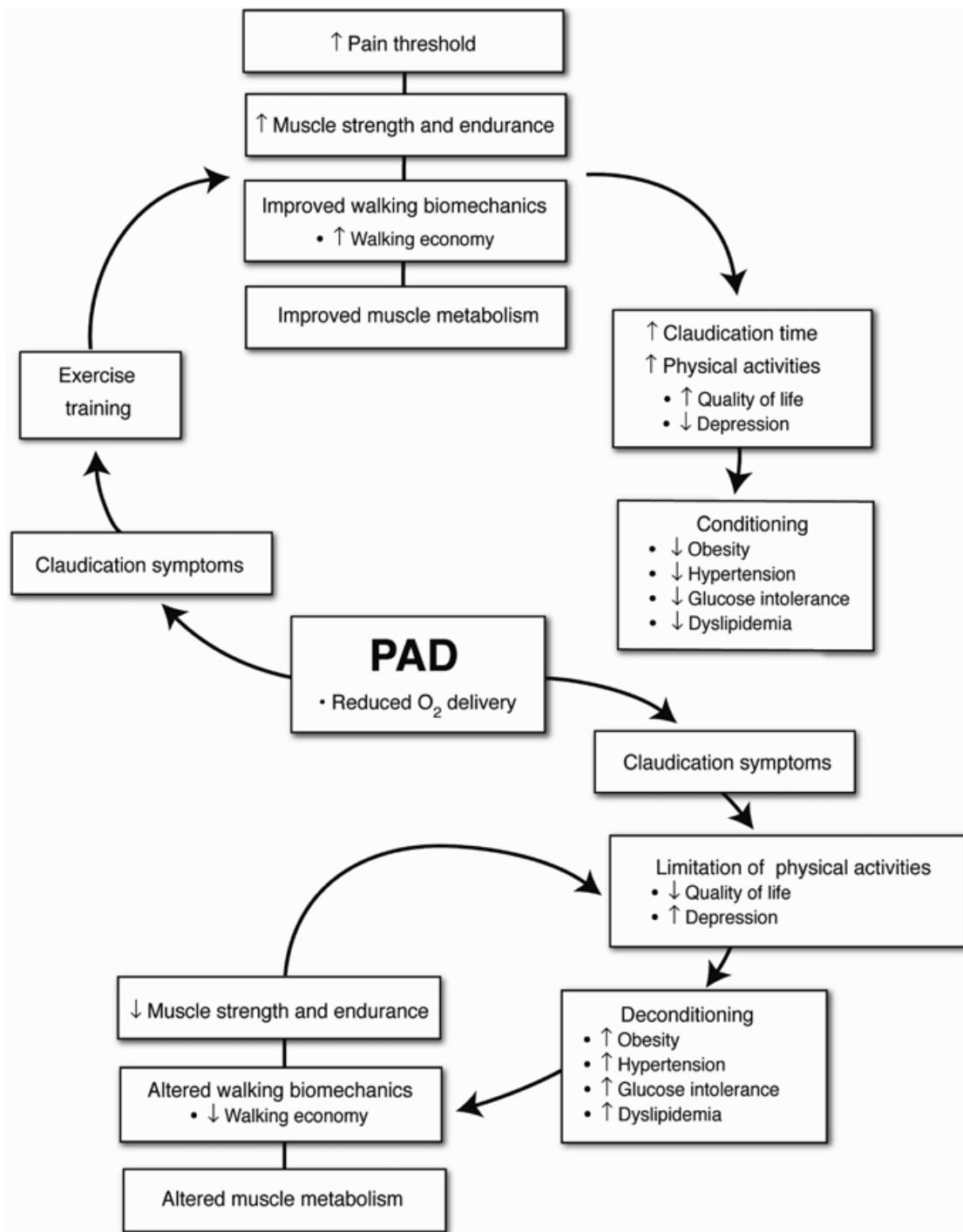


Figure 2.1: The cycle of disability and the benefits of exercise training in patients with PAD and IC. Reproduced with permission from Milani and Lavie (2007).

A problem for clinicians is that despite the wealth and quality of evidence demonstrating the effectiveness of exercise in the treatment of IC a number of patients do not adhere to exercise regimes or follow the advice to take regular independent exercise (Hamburg and Balady 2011). Despite this, there are a limited number of studies investigating adherence to

exercise therapy in patients with PAD and IC and even fewer that examine the psychosocial factors associated with motivation and adherence to exercise.

---

#### 2.4.2: Pharmacological Therapy:

---

Patients with PAD and IC should all receive pharmaceutical and lifestyle treatment for their cardiovascular risk factors (Norgren et al 2007). A number of pharmaceutical interventions have been shown to be successful in increasing walking distance in patients with IC including cilostazol, pentoxifylline, naftidrofuryl, carnitine, propionyl-L-carnitine and lipid lowering drugs (Norgren et al 2007). The mechanisms of action of each of these interventions, the supporting evidence and any reported side effects will now be discussed.

---

##### 2.4.2.1: Cilostazol:

---

Cilostazol is a phosphodiesterase III inhibitor with vasodilator, metabolic and antiplatelet activity (Norgren et al 2007). Cilostazol is a direct arterial vasodilator which also inhibits platelet aggregation and has antithrombotic, antimitogenic and cardiogenic properties (NICE 2009; O'Donnell et al 2009). Cilostazol mechanisms of action are still under debate but it is accepted that it improves blood flow to the peripheral tissues in patients with IC, improving the oxygenation of the muscles and thus reducing IC pain (O'Donnell et al 2009). Cilostazol has the best overall evidence for treatment benefit in patients with IC. In a meta-analysis of six randomised, controlled trials (RCT) it has been shown to have a net benefit over placebo of 50-70 metres in peak treadmill walking performance (Regensteiner et al 2002). It was also shown to significantly improve QoL as measured by the Walking Impairment Questionnaire (WIQ) and SF-36. These are significant and useful treatment effects in patients with PAD and IC. However, the side effects of the drug include headache, diarrhoea and heart palpitations. In addition, it does not reduce the rates of cardiovascular events and cardiovascular morbidity compared to placebo (Pratt 2001) and cannot be given to patients with congestive heart failure due to its mechanisms of action.

---

##### 2.4.2.2: Pentoxifylline:

---

Pentoxifylline lowers fibrinogen levels, improves red cell and white cell deformability and thus lowers blood viscosity (Norgren et al 2007; Jacoby and Mohler 2004). This lower



viscosity improves the perfusion of tissues distal to the atherosclerotic vessels, which in turn allows increased aerobic metabolism and thus prolongs the time to onset of IC pain. The evidence supporting the use of Pentoxifylline is somewhat inconsistent. Meta-analyses have not demonstrated unequivocal results although Pentoxifylline is a registered and prescribed medication for IC pain in the UK and Europe (Hood et al 1996; Moher et al 2000). Both studies concluded modest improvements in treadmill walking performance and functional status compared to placebo although the clinical benefits are questionable (Hood et al 1996; Moher et al 2000; Norgren et al 2007). Reported adverse reactions include dizziness, headache, dyspepsia, nausea and vomiting. It is contraindicated in patients with recent cerebral or retinal haemorrhage (Jacoby and Mohler 2004).

#### 2.4.2.3: Naftidrofuryl:

---

Naftidrofuryl is a 5-hydroxytryptamine type 2 antagonist which may improve muscle metabolism, and reduce erythrocyte and platelet aggregation (Norgren et al 2007). Similar to Cilostazol, Naftidrofuryl reduces IC pain by increasing blood flow to the tissues, but it is also proposed to improve aerobic metabolism in the muscles thus prolonging the time before the build up of products of anaerobic metabolism and thus IC pain. The efficacy of Naftidrofuryl has been reported in one meta-analysis in 1994 (Lehert et al 1994) and more recently, by Kieffer et al (2001) and Spengel et al (2002). It has been shown to increase treadmill walking distance by 26% and produce improvements in QoL measures compared to placebo. The reported side effects of Naftidrofuryl are minor with the most common being mild gastrointestinal disorders with some reports of headache, dizziness, insomnia and hepatitis (Jacoby and Mohler 2004; Norgren et al 2007).

#### 2.4.2.4: Carnitine and Propionyl-L-Carnitine:

---

Carnitine and Propionyl-L-Carnitine work by interacting with skeletal muscle oxidative metabolism, reducing the impact of IC on walking performance in a similar way to Naftidrofuryl (Norgren et al 2007). Two multicentre trials have investigated the effects of Propionyl-L-Carnitine on treadmill walking distance (Brevetti et al 1999; Hiatt et al 2001). It was reported to increase initial and maximal treadmill walking distance and improve

reported QoL, compared with placebo. Reported side effects are diarrhoea, increased appetite, body odour and rash.

---

#### 2.4.2.5: Lipid lowering drugs (Statins):

---

Statins lower the lipid content of the blood by reducing the production of lipids in the liver. Statins are thought to work in PAD and IC by improving endothelial and metabolic abnormalities secondary to atherosclerosis (Norgren et al 2007). Currently, the evidence for the use of Statins in PAD and IC is limited but the initial results are promising. Two studies have reported improved treadmill walking distance after 3 months, 6 months and 1 year (Mohler et al 2003; Mondillo et al 2003). The side effects again are rare and include headaches, abdominal pains, 'pins and needles', bloating, diarrhoea and nausea.

---

#### 2.4.3: Limitations with the Current Management of PAD and IC:

---

Currently, non-surgical management of PAD and IC consists of management of risk factors with exercise therapy and pharmacological interventions. Both of these management strategies have been shown to be successful at increasing walking distance and decreasing the rate of further complications (Leng et al 2000; Norgren et al 2007). These management strategies however, are not without their limitations. As mentioned in section 2.4.1, adherence to exercise therapy has been identified as a problem. Also, pharmacological interventions are expensive, can cause side effects and damage to the internal organs (Squires et al 2011). These issues will be discussed in turn with specific reference to the central research aim of this thesis: the possible effects of TENS for patients with PAD and IC.

---

##### 2.4.3.1: Adherence to Exercise Therapy:

---

Exercise therapy has numerous benefits for patients with PAD and IC. However, patient adherence has been identified as an issue (Hamburg and Balady 2011). There are a limited number of studies that have investigated long-term exercise habits in IC patients. Bartelink et al (2004) retrospectively examined walking exercise habits in patients with PAD and IC. They recruited 216 participants from local GP practices who had been diagnosed with atherosclerosis or PAD in the last 6 years and had the term 'claudication' present in their file. The study found that 52% of participants reported that they walked for the purpose of

exercise (n=113). Of those that reported walking for the purpose of exercise, only 44% (n=49) walked to the recommended intensity (i.e. through the pain), and just 25% (n= 28) walked to the optimum frequency (more than, or equal to 3 times a day). However, these results should be interpreted with caution as only 70% of the 216 respondents reported that they had been given advice about the need for exercise and the advice given was generally not very specific (Bartelink et al 2004). Also, the authors state the optimum frequency of exercise as more than, or equal to 3 times a day which contrasts with the current recommendations in the literature of exercising 3 times a week (Leng et al 2000; Bulmer and Coombes 2004; Bendermacher et al 2006; Hamburg and Balady 2011).

Kruidenier et al (2009c) recruited a consecutive sample of IC patients referred for community-based supervised exercise therapy (n=272) in an effort to examine the effectiveness of this type of exercise program. The program consisted of 2-3 times a week, 30 minute sessions for the first three months although the frequency of the sessions was reduced to 1 session every 2 weeks and 1 session every 8 weeks at 6 month and 12 month follow-up respectively (Kruidenier et al 2009c). At the one year follow-up, 52% (n=143) of the original participants had discontinued the program, giving a 48% compliance rate. This is a large dropout rate although it is comparable to that observed in a hospital setting (10-50%) (Regensteiner et al 1996; Kakkos et al 2005; Collins et al 2005; Kruidenier et al 2009c).

Bartelink et al (2004) and Kruidenier et al (2009c) reported the explanations given by the participants for poor exercise therapy adherence. Explanations for not starting exercising were either: co-morbidity; low pain tolerance; too painful or lack of supervision (Bartelink et al 2004). Participants in the study by Kruidenier et al (2009c) provided similar explanations (reported as reason and (% of dropouts)): satisfaction with the acquired walking distance (13%); unsatisfying results (18%); not motivated (15%); non-vascular comorbid disease (34%); and other reasons (not detailed in the study) (20%) (Kruidenier et al 2009c). Roche et al (2005) reported similar findings with 52% of participants interviewed citing IC pain as the reason they discontinued walking. These findings suggest a complex disease process and multifaceted psychosocial factors affecting motivation for exercise therapy. Nevertheless, a common theme amongst the studies was the influence of pain (Bartelink et al 2004; Roche

et al 2005; Kruidenier et al 2009c). The only study of the three that further examined the nature of the pain experienced was that of Roche et al (2005). They employed the McGill Pain Questionnaire (MPQ) to elicit subjective description of the quality and intensity along with separate psychosocial questionnaires. Preliminary analysis suggested that the pain experience of IC was severe, unique and associated with specific psychosocial factors (Roche et al 2005). A detailed examination of the IC pain experience, and its effects on walking performance is therefore indicated. This detailed knowledge of the pain experience is essential firstly, to begin to understand the impact of the disease and how IC pain experience could relate to exercise adherence and secondly, to begin investigation of possible adjunctive management strategies.

#### 2.4.3.2: Side Effects, Cost-Effectiveness and Mechanisms of Action of Pharmacological Therapy:

---

The pharmaceutical interventions for PAD and IC all have reported side effects. These range from headaches and dizziness to heart palpitations and diarrhoea. Some of the medications mentioned are also contraindicated in conditions common to the IC patient population due to increased mortality rates. In addition, there is a chance of drug interactions due to polypharmacy. These interactions can have significant risks for the patient, potentially causing permanent damage to their internal organs (Pratt 2001). In addition, the cost effectiveness of pharmacological intervention has been questioned when compared to exercise therapy (Lee et al 2007).

Squires et al (2011) conducted a systematic review and economic evaluation of IC medications compared to non-vasoactive medications in patients with PAD and IC. Twenty-six randomised controlled trials (RCTs) met the inclusion criteria and meta-analysis was performed for measures of walking distance. Cilostazol and naftidrofuryl oxalate were found to increase maximum walking distance from baseline compared to placebo. Side effects reported for all medications included headaches and gastrointestinal difficulties. There was no difference in serious adverse events (cardiovascular events and mortality) between IC medications and placebo although follow-up was limited in the included studies (maximum 24 weeks). For cost-effectiveness, naftidrofuryl oxalate was found to be best with a cost per

'Quality-Adjusted Life-Year' (QALY) gained of approximately £6070 compared with no treatment (Squires et al 2011).

Lee et al (2007) examined the cost-effectiveness of supervised exercise therapy (3 sessions a week for 12 weeks) compared to conservative medical therapy (antiplatelet therapy, smoking cessation advice and support, and management of hypertension, hypercholesterolaemia and diabetes) on measures of walking performance and health-related quality of life. This three-month exercise programme was associated with a gain of 0.027 QALYs per year above conservative medical therapy. This results in a cost per QALY of £1780, considerably less than reported with pharmaceutical management (Lee et al 2007).

In addition, current pharmacological treatment of IC aims to delay the onset of IC pain by altering physiological factors in the limbs, thus delaying the creation of the resulting ischaemic environment (Regensteiner et al 2002; Norgren et al 2007). Studies on patients with IC have found that when patients with IC walk 'through' pain, i.e. endure the ischaemic environment in their limb(s), this helps to encourage the formation of collateral vessels (arteriogenesis), increase cellular oxygen uptake from the blood, improve endothelial function and metabolic adaptations in skeletal muscle (Leng et al 2000; Stewart et al 2002). As pharmacological treatments work by delaying the onset of ischaemia, patients with IC may not be as encouraged to walk 'through' an ischaemic environment. Therefore, they may not gain the full benefits of arteriogenesis and any alterations in the physiology of the peripheral tissues that are associated with enduring ischaemia. Conversely, exercise therapy that encourages patients to regularly walk to maximal pain tolerance will utilise these compensatory physiological mechanisms and possibly produce a longer-lasting treatment effect (Treesak et al 2004; Lee et al 2007).

---

#### 2.4.4: Summary of the Management of PAD and IC:

---

Management of PAD and IC centres on the slowing of the progression of atherosclerosis and thus is focussed on the modification of cardiovascular risk factors (SIGN 2006; Norgren et al 2007). Core aspects of this approach to management are exercise and pharmacological therapy. The evidence for the benefit of these interventions is considerable, although they

are not without limitations. Patient adherence to exercise therapy has been found to be an issue and pharmacological interventions can cause side effects and are costly. These issues inform both aims of the current research programme. A greater understanding of the IC pain experience could help to examine the reasons for the reduced adherence to exercise therapy. Also, if TENS intervention is found to have a hypoalgesic effect on IC pain, it may prove to be a safe, low-cost, non-pharmacological adjunctive treatment which could augment the current pharmacological management of IC and improve the adherence to exercise therapy.

## 2.5: CURRENT HEALTHCARE PROVISION FOR THOSE WITH PAD AND IC IN THE UK:

Recent commentary within the vascular literature has highlighted a lack of adherence with optimal management of PAD and IC (Belch et al 2003; 2007). Guidelines exist that detail the optimal management for patients with PAD and IC (SIGN 2006; Norgeren et al 2007). Nevertheless patients with PAD and IC in the UK are currently under-diagnosed and under-treated (Belch et al 2007).

Khan et al (2007) investigated the current provision of medical management for patients with PAD and IC in 23 different sites across the UK. This well-designed, prospective cohort study recruited 473 participants with PAD and IC attending specialised vascular outpatient clinics. Data collected included demographic and disease measures of function along with information about current management. The sample was representative of a PAD and IC population with common comorbidities of hypertension (54%), diabetes (20%) and coronary artery disease (29%) (Khan et al 2007). Management focussed on risk factor modification but this was found to be sub-optimal. Antiplatelet therapy, lipid-lowering agents and ACE-inhibitors are recommended in the guidelines (Table 2.1) although 30% of the sample were not prescribed an antiplatelet, 50% were not prescribed a statin and 75% did not receive ACE-inhibitors or other medication for hypertension (Khan et al 2007). These results indicate poor management of blood pressure and cholesterol. The researchers noted that of the 40% of the sample that continued to smoke, only 50% had tried to stop within 6 months prior to enrolment in the study. Of these participants only half had been offered nicotine replacement therapy or smoking cessation counselling indicating poor adherence with the

guidelines on smoking cessation for patients with PAD (Anthonisen et al 2005; Khan et al 2007). D'Souza et al (2008) also highlighted the sub-standard level of medical management of patients with PAD in the UK. When compared to patients with coronary heart disease who share the same risk factors and similar outcomes, patients with PAD were less likely to receive advice and support with smoking cessation, less likely to be prescribed anti-platelet or lipid-lowering medications and for those with diabetes, blood sugar management was inadequate (D'Souza et al 2008).

Similar evidence of sub-optimal management of PAD and IC in the UK was also found in relation to supervised exercise (another guideline recommendation). Makris et al (2012) aimed to investigate the provision of supervised exercise therapy for patients with PAD and IC worldwide. Electronic questionnaires were sent to vascular surgeons and 378 were completed representing 43 countries. The majority of responses were from Europe (95%) and of these, 34% were from the UK. The vascular surgeons surveyed reported a lack of access to supervised access to supervised exercise programs with only 30% of the overall sample having the ability to refer to a program. Within the UK alone, 36% reported access to supervised exercise programs. This compared poorly to the 100% of surgeons in the Netherlands and 67% in France that were able to refer their patients to a supervised exercise program (Makris et al 2012). In a separate, but similar questionnaire study that focussed solely on the UK, Shalhoub et al (2009) found that only 24% of the vascular surgeons that responded had access to a supervised exercise program.

Overall, current evidence suggests that the management of PAD and IC in the UK focuses on modification of cardiovascular risk factors and exercise therapy. This is in line with the current guidelines however, when compared to the management of medical conditions with a similar risk profile or when compared to other European countries, management of PAD and IC is inferior and supervised exercise therapy is an under-utilised tool despite high quality evidence of its cost-effectiveness (Shalhoub et al 2009).

## 2.6: CONCLUSION:

---

PAD is a cardiovascular disease characterised by widespread atherosclerosis. The cardinal symptom of PAD is IC. IC is the symptomatic manifestation of the atherosclerotic limitation of blood flow to the legs, causing pain, fatigue and/or cramping on muscle exertion. PAD and IC are currently managed through a number of strategies, primarily risk factor modification and exercise therapy. A number of barriers to the success of exercise therapy have been identified and the pain due to IC has been highlighted as a potential key factor.

Current treatment of IC is focussed on modifying cardiovascular risk factors and is mainly pharmaceutical. These management strategies are effective and have been found to result in an increase in walking distance and QoL. Nevertheless, any additional, adjunctive intervention that increases physical activity or engagement with exercise therapy with fewer side effects and minimal cost could be useful.



## 2.7: CHAPTER 2 SUMMARY:

---

The aim of this chapter was to outline the clinical problem of PAD and IC. This chapter has highlighted that PAD is common, debilitating and merely a manifestation of more general atherosclerosis. IC has been identified as the cardinal symptom of PAD and represents a collection of symptoms that develop in the lower limbs when walking. The central component of IC is pain. The experience of IC is related to considerable physical limitations and a decrease in quality of life. Nevertheless, the specific qualities of IC pain have not been fully examined. These factors contribute to the first aim of this thesis: to investigate the subjective description of the multidimensional qualities of ischaemic pain.

This chapter also discussed the current management of PAD and IC. Management is focussed on cardiovascular risk factor modification with the aim of slowing the progression of atherosclerosis whilst increasing function and quality of life. The management strategies employed in patients with PAD and IC are exercise therapy and pharmacological management. Issues have been identified however with adherence to exercise therapy and pharmaceutical treatment has been shown to be associated with side effects. Both aims of the thesis look to address these limitations in the management of IC. By investigating the subjective descriptions of IC pain, the reasons for the reduced compliance with exercise therapy may be explored. Also, by investigating the hypoalgesic effects of TENS on lower limb ischaemic pain, TENS could be identified as a possible safe, non-pharmacological and low-cost adjunctive intervention for IC pain. If successful in reducing the experience of IC pain and increasing walking performance, TENS may help to increase adherence to exercise therapy and augment the beneficial effects of current medical management of IC.

The next two chapters examine the two concepts related to the aims of the thesis: pain and TENS. Chapter 3 will discuss the multidimensional nature of pain, how it can be measured and the common psychosocial aspects of pain. Chapter 4 will explore the theory and evidence for the use of TENS as a hypoalgesic intervention. This discussion within these chapters aims to summarise the current understanding of each topic and explore how this can be utilised to help address the current clinical problem of PAD and IC.

## CHAPTER 3: PAIN

---

### 3.1: AIM OF CHAPTER 3:

---

The aim of this chapter is to explore and discuss the current understanding of pain. Definitions and concepts will be discussed (sections 3.2 to 3.4) followed by a more in-depth exploration of the measurement and description of pain and associated psychosocial factors (sections 3.5 and 3.6). Throughout this chapter, the knowledge and evidence highlighted will be discussed in relation to the clinical problem of IC.

### 3.2: DEFINITIONS OF PAIN:

---

Pain is a complex experience, unique to the individual (Coghill et al 2003; Vetter 2007). It can occur with tissue damage or in the absence of damage and its impact goes beyond perception (Becker et al 1997). There are two distinct aspects of the pain experience, nociception and the perception of pain. Nociception is the physiological process associated with perception of pain and can be defined as:

*“the neural process of encoding noxious stimuli”*

(Merskey and Bogduk 1994 p215)

Pain is a psychophysiological process related to the perception of an experience. The International Association for the Study of Pain (IASP) defines pain as:

*“an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”*

(Merskey and Bogduk 1994 p210)

Pain therefore includes, and is dependent on, psychological constructs such as expectations, past experiences, anxiety, suggestion and attention (Villemure and Bushnell 2002; Wiech et al 2008).

### 3.3: THEORIES OF PAIN:

---

Over the past 10 centuries, the understanding of pain has developed through a number of theories. One of the earliest theories was ‘Specificity Theory’, proposed by Avicenna in the 11<sup>th</sup> century and René Descartes in the 17<sup>th</sup> century. They proposed that there were specific

nerve endings that processed each different sensation e.g. touch, temperature and pain (Brooks and Tracey 2005; Tashani and Johnson 2010).

In 1955, Sinclair and Weddell proposed the 'Peripheral Pattern Theory' (Sinclair 1995). They proposed that all nerve fibre endings are similar and that pain is produced by the intensity of stimulation e.g. slight stimulation represents touch and intense stimulation represents pain.

Ten years later, Melzack and Wall published their theory named 'Gate Control Theory' in the journal *Science* (Melzack and Wall 1965). This was a major step forward in the understanding of pain and specifically the modulation and facilitation of nociception in the spinal cord. The theory was based on much of the previous work. However it also incorporated the psychosocial aspects of pain perception.

Melzack and Casey published an addition to the 'Gate Control Theory' that proposed three specific dimensions of pain (Melzack and Casey 1968). They described sensory-discriminative, motivational-affective and cognitive-evaluative dimensions of the pain experience (Melzack and Casey 1968). There were however still limitations and conflict between the theories. For example, none was thought to thoroughly explain congenital insensitivity to pain or phantom limb pain (Melzack 1999).

In an effort to address the limitations of these previous theories, Melzack proposed a further theory, the 'Neuromatrix Theory' (Melzack 1999; 2001). This theory originated from the study of phantom limb phenomena and indications of central 'pattern generation' of pain (Melzack and Loeser 1978). Four general conclusions were presented (Melzack 1999; 2001):

1. The perceived 'body' is served by certain neural processes in the brain
2. The origins of the experience of pain lie in the neural networks of the brain
3. The body is perceived as a unity and 'self', distinct from other people
4. The brain processes that underlie the body 'self' are 'built in' by genetic specification

These conclusions led to the development of the theory of a body-self 'Neuromatrix'. The 'Neuromatrix' is proposed as a genetically built-in matrix of neurons for the whole body that produces characteristic nerve-impulse patterns that represent the body and all that is perceived. This matrix is initially determined genetically but is later sculpted by sensory inputs and is constructed from a widespread network of neurones that link the thalamus, cortex and limbic systems (Melzack 1999; 2001).

In terms of pain perception, the 'Neuromatrix Theory' suggests that pain arises from the output from the central matrix, termed a 'neurosignature'. The 'neurosignature' is the result of pattern recognition where genetic and sensory influences are mixed together with sensory inputs and cognitive events and the 'difference' from normal is recognised as pain (Melzack and Loeser 1978; Melzack 1999; 2001).

An understanding and appreciation of these theories of pain is important in achieving the aims of this thesis. To be able to fully examine the subjective descriptions of ischaemic pain and investigate the effects of TENS, these theories will be useful as a framework through which the different aspects of the pain experience can be explored. Nevertheless, in practice, these theories of pain offer too much detail to be useful in a clinical situation. Therefore, simpler concepts have evolved that are utilised for interpreting pain experience. In general, it is agreed that pain can be described in terms of four broad components: Nociception, Perception of pain, Suffering and Pain behaviours (Loeser and Melzack 1999; Melzack and Katz 2012). Nociception, as described above relates to the detection of tissue damage by specialised nerve endings (nociceptors). The perception of pain is often triggered by nociception but can occur in the absence of such input. Suffering is the negative response to pain or the associated fear, anxiety or stress. Pain behaviours are the outward display of the internal experience of pain and suffering (Loeser and Melzack 1999; Asghari and Nicholas 2001). These factors are essential and will be considered when interpreting ischaemic pain within this thesis.

### 3.4: CLASSIFICATION OF PAIN:

---

In addition to this simplified method for interpreting pain, general classifications of pain have developed. Pain is commonly described relating to its temporal nature i.e. acute or chronic. Acute pain describes pain that is limited by time and usually has a defined cause (Merskey and Bogduk 1994; Walsh et al 2009). It can be sudden in onset and may be mild, moderate or severe, but usually disappears when healing has taken place. It can serve as a protective function for the body, which alerts an individual to potential damage and can encourage rest of the affected part in order to promote healing (Melzack and Katz 2012).

Chronic pain can be defined as: 'daily pain reoccurring for more than 6 months, usually beyond the time for normal organic healing and is associated with negative psychosocial effects' (Vlaeyen et al 1995; Crombez et al 1999). Chronic pain may begin as acute pain but tends to last over an extended period of time, is linked to chronic pathological processes and can cause suffering in multiple systems (Merskey and Bogduk 1994). Unlike acute pain, its cause may be unknown or if known cannot be eliminated. This intractable pain has no biological value and can affect a person psychologically, emotionally and spiritually, as well as physically (Autton 1986; Villemure and Bushnell 2002; Wiech et al 2008).

The concept that chronic pain should be viewed as a disease in its own right has been gathering momentum over the past decade (Niv and Devor 2004; Siddall and Cousins 2004; Tracey and Bushnell 2009). This has resulted from the creation of a critical mass around the biopsychosocial model of health and the recognition that pain, and especially chronic pain, is a 'state' (persistent pain over time) rather than a 'symptom of something' (Croft et al 2010).

IC can be classified as a chronic pain syndrome and as such will be associated with individual psychological and psychosocial factors that have developed over time. This is an important concept to appreciate and may impact on the examination of laboratory and clinical ischaemic pain. It could be theorised that, compared to laboratory ischaemic pain, clinical ischaemic pain will be affected to a greater degree by psychosocial factors. Ultimately, what

is important in achieving the aims of this thesis is that all of these multidimensional factors of the pain experience are recorded and measured.

### 3.5: MEASUREMENT OF PAIN:

---

This section will discuss some of the methods that can be used to measure these aspects of pain. As discussed, pain is a personal, subjective experience that is influenced by cultural learning, the meaning of the situation, direction of attention and other psychological variables (Melzack and Wall 1996). When attempting to measure the experience of pain, two main types of measure have emerged as key components to any assessment. The Visual Analogue Scale (VAS) and Numerical Rating Scales (NRS) have emerged as single ratings of pain that encompass the other dimensions in a format that is easy to use and comprehend. The McGill Pain Questionnaire (MPQ) also measures pain intensity although due to the method of selecting adjectives that describe the person's pain, it can also be used as a measure of pain quality or the 'language of pain' (Katz and Melzack 1999).

Unlike many major chronic pain syndromes such as cancer pain, arthritis and post-surgical pain (Graham et al 1980; Roche and Heim 1997; Roche et al 2003; Bruce et al 2004; Ngamkham et al 2012), the qualitative nature of IC pain has not been explored. To achieve the aim of this project and examine the subjective description of IC pain, it is important that the intensity and quality of pain is measured and analysed.

---

#### 3.5.1: The Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS):

---

A VAS is a 100mm horizontal, or vertical line with two boundaries and anchors representing "no pain" and "worst pain imaginable". Responders are asked to make a mark somewhere along the line that represents their symptoms. Most commonly they are asked to rate their "current pain" or "pain in the last 24 hours" (Hawker et al 2011). The score is determined by using a ruler to measure the distance (mm) between the "no pain" anchor and the responder's mark on the line.

The VAS is used to measure pain in diverse adult populations and has been found to be sensitive to change (Jenkinson et al 1995; Williamson and Hoggart 2005) and closely

correlate with verbal and numerical ratings of pain (DeLoach et al 1998, Briggs and Closs 1999; Bijur et al 2003).

A NRS is similar to the VAS in that it is a one-dimensional measure that employs anchors of “no pain” and “worst pain imaginable”. Responders are asked to verbally “rate their pain on a scale between 0 and 10, where 0 represents no pain and 10 represents the worst pain imaginable”. The NRS most commonly consists of 11 levels (0-10) however; there are versions with 21 (0-20) or 101 (0-100) levels also.

Similar to the VAS, the NRS has been shown to be sensitive to change and relates to other measures of pain (Bolton and Wilkinson 1998; Williamson and Hoggart 2005). Jensen et al (1994) compared seven different measures of pain intensity, including 101-, 21- and 11-point NRS, in an effort to determine how many levels are required in a pain intensity scale to reliably measure pain with optimum sensitivity. The authors found that all measures were highly correlated in 124 mixed chronic pain patients and that little sensitivity was lost when using 11 or 21 levels compared to 101. They also found that when using the 101-point NRS, patients often selected numbers that were multiples of 5 or 10 and thus were using as if it were a 21-point scale (Jensen et al 1994).

Overall, both the VAS and the NRS have been shown to be sensitive and reliable measures of pain intensity. The NRS has an added benefit due to its ease of use. It can be administered verbally and in writing and is simpler to score (Hawker et al 2011).

---

### 3.5.2: The McGill Pain Questionnaire (MPQ):

---

Melzack and Casey (1968) suggested that there are three dimensions of pain experience: sensory-discriminative, motivational-affective and cognitive-evaluative. Following the development of this theory and the subsequent examination of the language used to describe pain the McGill Pain Questionnaire (MPQ) was conceived (Melzack and Torgerson 1971; Melzack 1975).

Based on this theoretical principle Melzack and Torgerson (1971) conducted a two-part study on the specifying qualities of pain. They asked physicians and university graduates to classify 102 words, obtained from the clinical literature, into small groups that describe the different aspects of the experience of pain. On the basis of this data, the words were categorised into three major classes (sensory, affective and evaluative) and 16 subclasses. The classes were based on a) words that describe the sensory qualities of pain; b) words that describe the affective qualities of pain in terms of tension, fear and punishment; and c) evaluative words that describe the subjective, overall intensity of the total pain experience (Melzack and Torgerson 1971; Melzack and Katz 2012). In the second part of the study, they attempted to determine the intensity of the words included in each subclass. Again, they asked physicians, graduates but patients as well to assign an intensity value to each word, from “least pain” to “worst pain”. Although the values on the intensity scale chosen in each group were different, they all agreed on the position of the words relative to each other. Using the data from these studies, Melzack constructed the MPQ as an experimental tool for use in studies on pain management (Melzack 1975).

The MPQ consists of 78 pain adjectives separated into 20 subclasses describing different aspects of the pain experience, and ranked within these subclasses in order of intensity (see Table 3.1). Responders are asked to choose one adjective from each subclass that describes their pain or, if none of the adjectives in a subclass adequately describes their pain, they are instructed to leave it blank. These subclasses are divided into four major groups: sensory (subgroups 1-10), affective (11-15), evaluative (16) and miscellaneous (17-20), referring to the sensory-discriminative, affective-motivational and cognitive-evaluative dimensions previously described.

Despite its descriptive, qualitative nature, the MPQ can also produce a single quantitative score of pain intensity, which is termed the Pain Rating Index (PRI). This is calculated by summing the score for each subclass. Melzack et al (1985) further developed this quantitative measure by adding a weighting factor for each subclass.



Table 3.1: 20 Subgroups of the MPQ and the ranked pain descriptors (Melzack 1975)

<b>1- Temporal</b>	<b>2- Spatial</b>	<b>3- Punctuate Pressure</b>	<b>4- Incisive Pressure</b>
1. Flickering 2. Quivering 3. Pulsing 4. Throbbing 5. Beating 6. Pounding	1. Jumping 2. Flashing 3. Shooting	1. Pricking 2. Boring 3. Drilling 4. Stabbing 5. Lancinating	1. Sharp 2. Cutting 3. Lacerating
<b>5- Constrictive Pressure</b>	<b>6- Traction Pressure</b>	<b>7- Thermal</b>	<b>8- Brightness</b>
1. Pinching 2. Pressing 3. Gnawing 4. Cramping 5. Crushing	1. Tugging 2. Pulling 3. Wrenching	1. Hot 2. Burning 3. Scalding 4. Searing	1. Tingling 5. Itchy 6. Smarting 7. Stinging
<b>9- Dullness</b>	<b>10- Sensory Miscellaneous</b>	<b>11- Tension</b>	<b>12- Autonomic</b>
1. Dull 2. Sore 3. Hurting 4. Aching 5. Heavy	1. Tender 2. Taut 3. Rasping 4. Splitting	1. Tiring 2. Exhausting	1. Sickening 2. Suffocating
<b>13- Fear</b>	<b>14- Punishment</b>	<b>15- Affective Miscellaneous</b>	<b>16- Evaluative</b>
1. Fearful 2. Frightening 3. Terrifying	1. Punishing 2. Gruelling 3. Cruel 4. Vicious 5. Killing	1. Wretched 2. Blinding	1. Annoying 2. Troublesome 3. Miserable 4. Intense 5. Unbearable
<b>17- Miscellaneous</b>	<b>18- Miscellaneous</b>	<b>19- Miscellaneous</b>	<b>20- Miscellaneous</b>
1. Spreading 2. Radiating 3. Penetrating 4. Piercing	1. Tight 2. Numb 3. Drawing 4. Squeezing 5. Tearing	1. Cool 2. Cold 3. Freezing	1. Nagging 2. Nauseating 3. Agonising 4. Dreadful 5. Torturing

### 3.5.2.1: Psychometric Properties:

---

Since its development, the MPQ has been shown to be a valid and reliable measure of acute and chronic clinical pain and laboratory-induced pain (Melzack 1983; Wilkie et al 1990).

#### Reliability:

---

The MPQ has been shown to reliably measure quality and intensity of pain over time (Graham et al 1980; Love et al 1989; Roche et al 2003; Broderick et al 2008). Graham et al (1980) investigated the reliability of the MPQ in a group of 36 community-dwelling patients with cancer pain. All participants completed the MPQ describing their current pain, once a week for 5 weeks. Participants selected similar adjectives and PRI scores were comparable at each time point (Graham et al 1980). Broderick et al (2008) found that the 3 items from the MPQ were found to have good test-retest reliability over 1 day recall ( $r = 0.81$ ) but this became poorer when the recall was over 7 days ( $r = 0.59$ ) in a sample of patients with rheumatology pain. Generally, the MPQ has been shown to have good test-retest reliability in a variety of populations ( $r > 0.70$ ) (Melzack et al 1975; Graham et al 1980; Love et al 1989; Roche et al 2003; Broderick et al 2008).

#### Validity:

---

The MPQ has content validity. Respondents regularly utilise all 20 subclasses of adjectives and those with the same pain syndrome select similar clusters of words to describe their pain experience, regardless of disease severity (Dubuisson and Melzack 1976; Burckhardt 1984).

Turk et al (1985) examined the factor structure of the MPQ in a varied sample of 168 patients with chronic pain and concluded that the PRI lacked discriminant validity. The authors examined the three-factor structure (sensory, affective and evaluative) of the PRI and found that all three were highly inter-correlated and therefore not distinct. The recommendations were therefore to use the total PRI score as this will reflect changes in any of the subcategories or examine the patterns of adjective selection in the individual subclasses. These conclusions are supported and expanded by Holroyd et al (1992) who reported that despite a four-factor model of the PRI (2 sensory, 1 affective and 1 evaluative)

best explaining covariance, the high inter-correlation between the factors cast doubt on the discriminant validity of the PRI subcategories.

Criterion and construct validity of the MPQ has also been established. The number of words chosen has been found to correlate significantly with VAS scores in arthritis and post-operative pain (Papageorgiou and Badley 1989; Katz et al 1994), and with measures of health-related quality of life in osteoarthritis (Gandhi et al 2010).

Use of the MPQ has been questioned due to the level of literacy and comprehension required to complete it correctly. The descriptors included in the MPQ were selected by scientists and arose from words patients used to describe pain 40 years ago and therefore may not possess the same meaning, or at least common usage today (e.g. lancinating, rasping). Also, the adjectives used do not necessarily encompass all terms in current usage to describe pain (Skevington 1995; Hawker et al 2011).

#### Sensitivity:

The MPQ has been found to be sensitive to change in clinical and laboratory pain populations. In post-surgical pain, the PRI of the MPQ was found to be less sensitive to change in pain intensity than a VAS or a verbal rating scale however; this was over a very short time period (4 hours) (Jenkinson et al 1995). In laboratory pain, the MPQ has been shown to detect differences between type and intensity of pain, both with PRI scores and patterns of words chosen (Klepac et al 1981; Chen and Treede 1985).

#### 3.5.2.2: Describing Pain Syndromes with the MPQ:

In addition to being a multidimensional measure of pain intensity, the MPQ has been used to examine the characteristics of common pain conditions. Dubuisson and Melzack (1976) utilised the MPQ to examine the description of eight pain syndromes. By using multi-group discriminant analysis they were able to identify specific adjectives that commonly describe each pain experience. Table 3.2 details the adjectives chosen by more than a third of participants in six of these pain syndromes. Commonalities of description have been found in patients with phantom limb pain, labour pain, cancer pain, toothache pain and arthritis

pain (Graham et al 1980; Melzack et al 1981; Grushka and Sessle 1984; Katz and Melzack 1991; Katz 1992; Roche and Heim 1997; Roche et al 2003).

The MPQ has now become a frequently used tool in the assessment, diagnosis and management of complex, chronic pain syndromes (Melzack 1987; Wright et al 2001) but has not been used to describe IC pain.

The PRI scores for different pain syndromes have also been examined. In order of severity, PRI scores were: causalgia = 42; labour pain = 29-38; back pain = 27; cancer pain = 26; phantom limb pain = 25; post herpetic neuralgia = 22; toothache = 19; fracture = 19; arthritis = 18; and tissue damage including cuts, bruises and sprains = 16-21 (Melzack 1984). PRI is however a crude measure of overall pain intensity. These statistics do provide an indication of the number of pain syndromes that have been investigated using the MPQ. The specific qualities of IC pain have not yet been explored. Employing the MPQ in a sample of patients with PAD and IC would allow an investigation into the common and distinctive characteristics of the pain experience. The results of such a study would help to inform further investigation of management strategies aimed at targeting specific aspects of the pain experience.

Table 3.2: MPQ adjectives chosen by more than 33% of participants for menstrual, arthritic, labour, dental, back and cancer pain (adapted from Dubuisson and Melzack 1976).

Syndrome	Number	Sensory	Affective	Evaluative
Menstrual Pain	25	Cramping Aching	Tiring Sickening	
Arthritic Pain	16	Gnawing Aching	Exhausting	Annoying
Labour Pain	11	Pounding Shooting Stabbing Sharp Cramping Aching	Tiring Exhausting Fearful	Intense
Dental Pain	10	Throbbing Boring Sharp	Sickening	Annoying
Back Pain	10	Throbbing Shooting Stabbing Sharp Cramping Aching Heavy Tender	Tiring Exhausting	Unbearable
Cancer Pain	8	Shooting Sharp Gnawing Burning Heavy	Exhausting	Unbearable

### 3.5.3: The Short-Form MPQ (SF-MPQ):

Due to the need for a quicker method of measuring the qualities of pain, a 'short-form' of the MPQ has been developed (Melzack 1987). The Short Form MPQ (SF-MPQ) was felt to be important for research where brief assessments of multidimensional pain intensity were required e.g. in the evaluation of pharmaceuticals. The shortened version contains 15 adjectives representing 11 sensory and 4 affective categories. These adjectives were chosen

as the most popular descriptors utilised to describe a range of pain conditions (Melzack 1987; Fernandez and Towery 1997).

The SF-MPQ was found to correlate highly with the MPQ and is sensitive to change (Melzack 1987; Dudgeon et al 1993; Grafton et al 2005). It has also been shown to have test-retest reliability over 5 days in patients with arthritic joint pain (ICC = 0.88-0.96) (Grafton et al 2005). However, dissimilar to the full version, the SF-MPQ has been shown to have only a two-factor structure (sensory and affective) (Wright et al 2001).

Overall it is judged to be easier to use and takes less time to administer than the full MPQ. These properties make it useful when investigating change from baseline in order to evaluate the effect of an intervention (Grafton et al 2005). However, when investigating the subjective qualities of a pain experience, the SF-MPQ is limited in its ability to explore the nuances of the full experience (van Wijk and Hoogstraten 2002). This is primarily because it does not include words commonly used to describe pain and also does not measure evaluative components (Dudgeon et al 2005).

Due to these limitations, the SF-MPQ is not ideal when investigating the multidimensional nature and subjective description of a pain experience such as IC. The full version of the MPQ is more suited as it includes a greater range of pain descriptors that encompass more components of the pain experience. As the aim of the current study is to examine the subjective description of the IC pain experience, the full version of the MPQ is therefore more appropriate to employ compared to the SF-MPQ.

---

#### 3.5.4: Summary:

---

Overall, the MPQ is recommended for the assessment of clinical and laboratory pain. It is most useful when examining the descriptive qualities of a pain experience and should be used in conjunction with a VAS or other simpler measure for evaluation of a change in pain intensity over time. As this thesis aims to record the subjective descriptions of IC pain and examine the effect of TENS on this pain experience, the MPQ and a NRS are both required.

The MPQ will function to measure the descriptive qualities of the pain and the use of a NRS will allow examination of the effects of TENS over time.

As discussed in section 3.4, chronic pain syndromes are associated with negative psychosocial effects (Crombez et al 1999). An exploration of a chronic pain experience would not be complete therefore without investigation of these psychosocial aspects. As identified in Chapter 1, IC has been shown to be associated with negative psychosocial factors, chiefly depression. It is therefore important to have an understanding of the origin and nature of these factors when examining IC pain.

### 3.6: PSYCHOSOCIAL ASPECTS OF PAIN:

---

Pain, and especially chronic pain represents a stressful situation that extends beyond merely enduring the sensation. Thus living with chronic pain can impact many aspects of the sufferer's life and cause significant emotional effects (Turk and Monarch 2002). Most commonly, the primary focus of someone in pain is the elimination of the experience. In chronic pain, when this is not always possible the failure in achieving relief can lead to negative emotions (Main and Watson 1999). In addition, the sufferer does not experience this in isolation. The complex interactions with significant others, healthcare professionals and their respective environments can both positively and negatively impact these emotions and thus the pain experience (Turk and Monarch 2002). These emotions, cognitions and social interactions have been investigated in numerous chronic pain conditions and are collectively termed 'psychosocial aspects' of pain (Keefe et al 2004).

It is still debated whether it is psychosocial aspects of pain that sensitise patients to the development of chronic pain or whether they are a consequence of the pain experience (Large 1996). Nevertheless, it has been shown that they contribute significantly to functional disability, independent of physiological measures and pain severity in a wide range of chronic pain syndromes (Main and Watson 1999; Karoly and Rueblman 2007). It is important therefore to acknowledge and appreciate the psychological and social aspects of any pain experience.

Psychosocial aspects of pain are multiple and multifaceted. There are however, a few key aspects that have been the focus of a considerable amount of research and have been found to impact on clinical pain. These factors will now be briefly reviewed and the current status of evidence summarised.

---

#### 3.6.1: Pain Catastrophising:

---

Pain Catastrophising can be defined as “an exaggerated negative orientation toward actual or anticipated pain experiences” (Gatchel et al 2007, p602). Pain catastrophising can be measured using a subscale of the Coping Strategies Questionnaire (CSQ) (Rosentiel and Keefe 1983) or the more focussed Pain Catastrophising Questionnaire (PCS) (Sullivan et al 1995). Factor analysis of the PCS has identified three second-order factors: rumination, magnification and helplessness (Sullivan et al 1995; Granot and Ferber 2005). These factors clearly indicate the components of pain catastrophising: thinking about, or ruminating on the pain, magnifying the threat value of pain and feeling helpless in the context of pain.

Research has identified pain catastrophising as one of the most important predictors of pain, accounting for between 7 and 39% of variance in the rating of pain intensity (Sullivan et al 2001; Geisser et al 1994; Sullivan et al 2006). Catastrophising has also been shown to be associated with a number of other health-related outcomes, independent of pain intensity. These include higher levels of healthcare usage (Gil et al 1992); longer hospital stays (Gil et al 1993); higher levels of disability (Martin et al 1996); increased use of medication (Jacobson and Butler 1996); increased motor pain behaviours (Keefe et al 1997); slower progress with rehabilitation (Kendell et al 2001); perception of pain intensity and disability when experiencing experimentally induced pain (Parr et al 2012).

---

#### 3.6.2: Pain-Related Fear:

---

Pain-related fear is closely associated with pain catastrophising (Gatchel et al 2007). Fear of pain is associated with beliefs that pain represents damage or significant harm to the body and beliefs that activities that cause pain should be avoided (Waddell et al 1993; Vlaeyen et al 1995; Geisser et al 2000; Crombez et al 2012).



Patients with high levels of pain-related fear have been shown to report higher levels of pain (McCracken 1997; Crombez et al 1999), score highly on self-report measures of disability and depression (McCracken et al 1992) and lower on measures of pain-related coping (McCracken and Gross 1993). An increase in reported fear of pain has also been shown to relate to changes in observed behaviour: avoidance of tasks (Swinkels-Meewisse et al 2003) and a decrease in speed of performance of tasks (Vlaeyen et al 1995).

---

### 3.6.3: Perceived Control and Pain Self-Efficacy:

---

Perceived control related to pain refers to “the belief that one can exert influence on the duration, frequency, intensity or unpleasantness of pain” (Gatchel et al 2007, p603). Self-efficacy has been conceptualised as an intrinsic motivational factor in learning (Bandura et al 2001; Eccles and Wigfield 2002). Perceived self-efficacy can be defined as “people’s beliefs about their capabilities to produce designated levels of performance that exercise influence over events that affect their lives” (Bandura 1994).

It is conceptualised that it is these beliefs that modify the meaning of the stimulus of pain and thus directly affect the appraisal of the threat of pain. High scores on self-report measures of pain self-efficacy have been shown to be related to lower levels of pain, lower levels of psychological distress and improved outcomes (Lorig et al 1989; Parker et al 1993; Buckelew et al 1994; Keefe et al 1997; Brekke et al 2003).

---

### 3.6.4: Helplessness and Depression:

---

Based on the theory of the learned helplessness model of depression (Abramson et al 1978), Helplessness refers to a focus on generalised, uncontrollable, long-term outcomes of chronic pain. It signifies an assumed ‘style’ where negative events such as chronic pain and its consequences are perceived as unpredictable and unavoidable.

Depression affects approximately 40-50% of patients with chronic pain (Romano and Turner 1985; Fishbain et al 1997; Dersh et al 2006). Although symptoms of depression are closely related to chronic pain, it is still argued whether depression is an antecedent or consequence of the experience of pain (Keefe et al 2004; Gatchel et al 2007).

---

### 3.6.5: Summary:

---

Recent and growing research has shown that psychosocial factors have both positive and negative effects on pain and disability in patients with chronic pain. There is strong evidence that supports the theories that pain catastrophising and pain-related fear are both related to 'poor adjustment' to pain. There is also strong evidence that increased level of pain self-efficacy are related to improved adjustment in the face of pain. What is still not known however, is the direction of these relationships i.e. is the experience of chronic pain an antecedent or consequence of the psychosocial factors?

For the purposes of the current project, it is important that when exploring the qualities of lower limb ischaemic pain and investigating the effects of TENS that these factors are considered and taken into account when interpreting the results observed.

### 3.7: CONCLUSION:

---

At present there is a wealth of literature examining the physiological causes and nature of PAD. Conversely, there is a dearth of literature examining the tangible manifestation of the most debilitating symptom of the disease: the pain of IC. A detailed understanding of the specific, multidimensional quality and intensity of the pain experienced and the associated psychosocial factors could be a step towards understanding, and ultimately managing, IC pain.

The MPQ is an ideal measurement tool with which to investigate pain description in patients with IC. Use of the MPQ will allow eliciting of a quantitative measure of intensity (PRI) whilst also recording the qualitative nature of the pain experienced i.e. the vocabulary chosen to describe the pain. This type of understanding of IC pain could help to enhance the development of tailored interventions.

### 3.8: CHAPTER 3 SUMMARY:

---

The aim of this chapter was to explore and discuss the current understanding of pain. This aim was achieved by discussing the definitions and theories of pain and how these have changed over time. The current understanding of pain is as a complex, multidimensional experience: the result and cause of multiple, complex interactions between physiological and psychological factors. The classification of pain as either acute or chronic was also discussed and related to the clinical problem addressed by the current project: chronic IC pain. Measurement of pain is focussed primarily on simple, single-rating scales that provide an overall indication of pain intensity although these scales are not able to provide detail regarding the specific qualities of pain. The MPQ uses the subjective description of pain to form a measure of intensity but that also allows some exploration of the specific qualities of the pain experience. Finally, the current understanding of the psychosocial aspects associated with pain was briefly discussed. Four different psychosocial constructs were identified that have been shown to be associated with pain. These aspects contribute positively and negatively to the experience of pain, adjustment to pain and pain-related disability.

The discussions within this Chapter inform both aims of the thesis. The theories and classification of pain help to frame the exploration of lower limb ischaemic pain within the current evidence base. The discussions relating to the measurement of pain help to establish the method with which to measure and explore the ischaemic pain experience and also how to evaluate the effects of TENS on this pain. Finally, psychosocial aspects of pain have been shown to be important in other chronic pain syndromes and will be important to measure when describing the ischaemic pain experience and examining the effects of TENS on IC pain.

## CHAPTER 4: TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS)

---

### 4.1: AIM OF CHAPTER 4:

---

The first two substantial chapters of this thesis have explored the perceived clinical problems associated with IC (Chapter 2) and this has been framed within the current understanding of pain (Chapter 3). This chapter aims to introduce the concept of TENS as a possible useful adjunctive intervention for IC pain.

The basic mechanisms of TENS will first be discussed (section 4.4) then the evidence for the use of TENS as a method of pain relief will be explored (sections 4.5 and 4.6). This discussion will inform the central aim of the thesis: to investigate the hypoalgesic effects of TENS for lower limb ischaemic pain. The contents of this chapter will influence the methods and interpretation of the results from the study of TENS for ischaemic pain.

### 4.2: NON-PHARMACEUTICAL INTERVENTIONS FOR IC:

---

As discussed, current management of IC is mainly pharmaceutical and somewhat ineffective, specifically for IC pain. A non-pharmaceutical, low-cost and easily applied intervention that allows patients to walk longer before the onset of pain and/or to walk longer while experiencing pain could be a useful adjunctive method of treatment. This could result in patients improving their exercise performance and engagement with exercise therapy. TENS is a potential modality for investigation.

---

#### 4.2.1: TENS:

---

TENS is a form of electrical stimulation that provides symptomatic pain relief that is used extensively within the health-care setting. It is a non-invasive modality; packaged in a small, portable unit that is easy to apply via small electrodes placed on the skin. It can be kept in a pocket or clipped to a trouser belt and is used widely and daily by patients with chronic pain to reduce their pain, improve their daily functioning and in some cases return to work (Johnson et al 1991; Sluka and Walsh 2003).

#### 4.3: HISTORY OF TENS:

---

TENS is defined as the application of electrical stimulation to the skin for purposes of pain control (American Physical Therapy Association 2001). The development of TENS as a hypoalgesic modality followed the publication of the Pain Gate Theory (Melzack and Wall 1965). Wall and Sweet (1967), in a study of spinal cord stimulation, demonstrated that high frequency electrical stimulation at an intensity which activated A $\beta$  afferent nerve fibres reduced neuropathic pain in a sample of chronic pain patients.

Since its inception, different stimulation parameters of TENS have been tested and employed clinically. This investigation of TENS has resulted in the efficacy of different stimulation parameters being tested and different neurophysiological mechanisms of action proposed (Claydon et al 2011).

#### 4.4: TENS MECHANISMS OF ACTION:

---

TENS acts by delivering pulsed electrical currents across the intact surface of the skin via electrodes (Johnson 2002). The theoretical foundation for this type of electroanalgesia builds on the mechanisms described in the 'Pain Gate Theory' (Melzack and Wall 1965). This theory proposed that there was a metaphorical 'gate' in the dorsal horn of the spinal cord, which could regulate the amount of incoming nociceptive information from the periphery via small diameter afferent nerve fibres. They proposed that this 'gate' could be effectively closed by a variety of other stimuli, such as: touch, pressure and electrical stimulation, which are carried by large diameter afferent fibres. This theory has been discussed and examined over the last four decades resulting in the development of a neurophysiological evidence base (Eriksson et al 1979; Eriksson et al 1985; Tulgar et al 1991; Garrison and Foreman 1994; Sluka and Walsh 2003; Radhakrishnan and Sluka 2005; Chen and Johnson 2010a; 2010b; 2011).

Due to technological advances, current TENS machines provide a range of possible ways that TENS can be delivered, with the different settings having different mechanisms of action (Johnson 2002; Walsh et al 2009). Two main stimulation patterns of TENS have been identified that work through distinct neurophysiological pathways of analgesia:

1. Conventional, or High-Frequency TENS (HF-TENS)
2. Acupuncture-Like, or Low-Frequency TENS (LF-TENS)

The mechanisms of action of each of these types of TENS stimulation will now be discussed in detail and related to the current problem of IC.

---

#### 4.4.1: High-Frequency TENS (HF-TENS):

---

HF-TENS is high frequency electrical stimulation delivered at low, non-noxious intensities. The typical stimulation parameters for HF-TENS are a frequency between 10 and 200Hz and a pulse width of 100-200 $\mu$ s (Johnson 2002). The intensity of the current is adjusted to provide a strong, but comfortable paraesthesia. This mode of TENS is sometimes termed 'high frequency, low intensity TENS' and is the most commonly used form of TENS in the clinical setting (Johnson 2002).

HF-TENS is proposed to act at the spinal segmental level by selectively activating large diameter mechanoreceptors (A $\beta$ -fibres), without concurrent activation of nociceptive A $\delta$ - and C-fibres or muscle efferents (Johnson 2002; Sluka and Walsh 2003). Selective activation of A $\beta$ -fibres inhibits nociceptive nerve transmission, through excitation of inhibitory interneurons, at the segmental level in the spinal dorsal horn, thus inhibiting A $\delta$ - and C-fibre stimuli transmission up the spinal cord.

One of the most important reported therapeutic characteristics of HF-TENS, which relates to this mechanism of action, is the rapid onset and offset of the induced analgesia (DeSantana et al 2008). Analgesia is commonly reported immediately after the stimulation has begun and it is lost less than 30 minutes after the machine is switched off. Thus, analgesia is present during HF-TENS stimulation but is lost shortly after the stimulation is ceased (Johnson 2002; Defrin et al 2005).

---

#### 4.4.2: Low-Frequency TENS (LF-TENS):

---

The typical stimulation parameters for LF-TENS are a frequency between 2 and 10Hz and pulse duration of 200-300 $\mu$ s (Johnson 2002). The electrodes are placed over a motor point

and the intensity of the current is adjusted to generate phasic muscle contractions. This mode of TENS is sometimes referred to as 'low frequency, high intensity TENS'. Due to the method of inducing analgesia, LF-TENS is uncomfortable and therefore often not well tolerated by patients in the clinical setting.

LF-TENS is low frequency stimulation (2-10Hz) delivered at high intensities, explained as: intensity that induces forceful but non-painful phasic muscle contractions at myotomes related to the origin of the pain (Eriksson and Sjolund 1976; Woolf and Thompson 1994; Johnson 2002). LF-TENS is proposed to act through extrasegmental mechanisms, promoting the release of endorphins (endogenous opioids) and inducing extrasegmental, generalised analgesia (Sluka and Walsh 2003). LF-TENS is theorised to selectively activate small diameter fibres (A $\delta$  or group III) arising from muscles (ergoreceptors) by the induction of phasic muscle contractions (Eriksson and Sjolund 1976). Ultimately, LF-TENS produces anti-nociception by activating descending neural pathways that inhibit nociceptive propagation through the spinal cord (endogenous opiates binding to opiate receptors on the spinal cord) and higher brain centres (Sjolund et al 1977; Barlas and Lundeberg 2006). Laboratory and clinical studies have shown that LF-TENS, unlike HF-TENS, produces delayed, but long-lasting analgesic action (Johnson et al 1991; Woolf and Thompson 1994; Walsh 1997). The delayed onset of analgesia is thought to be a result of the extrasegmental mechanism of action, as it takes longer to activate the descending neural pathways. Post-stimulation analgesia has also been reported and this is also thought to be a result of this systemic mechanism of action and the endogenous opiates providing a latent analgesic effect (Johnson et al 1991; Francis et al 2011). Therefore, LF-TENS appears not to induce analgesia immediately but takes a few minutes to provide effective pain relief. However, this pain relief continues for some time after stimulation has stopped.

#### 4.5: EVIDENCE FOR THE NEUROPHYSIOLOGICAL MECHANISMS OF TENS

---

Numerous studies have examined the neurophysiological mechanisms of TENS in both animal and human studies of experimental and clinical pain. Gradually, an understanding of the mechanisms of TENS is being elucidated.

---

#### 4.5.1: Animal Pain Models:

---

A detailed study by Garrison and Forman (1994) examined the effects of HF-TENS on spontaneous and noxiously evoked dorsal horn cell activity in an anaesthetised cat. They reported that HF-TENS application resulted in decreased spontaneous, and noxiously evoked cellular activity at the corresponding spinal level. The authors were unable to draw any conclusions relating to the role of supraspinal mechanisms, as the spinal cords used in their model were not intact.

Sluka et al (2005) also presented evidence of segmental inhibition with HF-TENS. In a rat model of inflammatory pain, they found that HF-TENS significantly reduced the concentration of neurotransmitters in the spinal cord associated with the transmission of pain (glutamate and aspartate). This action was extinguished by blockage of delta-opioid ( $\delta$ -opioid) receptors in the spinal cord and thus it was hypothesised that HF-TENS works by activating  $\delta$ -opioid receptors, reducing the release of neurotransmitters into the spinal cord (Sluka et al 2005).

The original hypothesis for the action of LF-TENS was the activation of A $\delta$  fibres and the resulting supraspinal release of endogenous endorphins and generalised hypoalgesia. This contrasted with the proposed mechanisms of HF-TENS to work through activation of A $\beta$  fibres and hypoalgesia purely through the gating mechanism in the spinal cord. A well-designed study by Radhakrishnan and Sluka (2005) however, has questioned these proposed mechanisms. In a rat model of hyperalgesia induced by local inflammation, the researchers showed that, by selective anaesthesia of cutaneous and deep tissue afferent fibres, both HF- and LF-TENS stimulate large diameter, deep tissue A $\beta$  fibres. It was only when the intensity of TENS stimulation was increased to twice the motor threshold that there was evidence of activation of A $\delta$  fibres. These results suggest that both types of TENS work through spinal inhibition of nociception, rather than through two distinct mechanisms.

Nevertheless, the same researchers also found evidence of supraspinal mechanisms and descending inhibition of nociception originating in the rostral ventral medulla (RVM). Stimulation of A $\beta$  fibres was found to result in activation of supraspinal mechanisms, and as



both types of TENS were found to stimulate these fibres, this suggests that both HF and LF-TENS activate both mechanisms of hypoalgesia and thus share mechanisms of action (Radhakrishnan and Sluka 2005). These findings have been supported by further study on a rat model of inflammatory pain, which found that both types of TENS activate the RVM and the midbrain (venterolateral periaqueductal grey) initiating opioid-mediated hypoalgesia (DeSantana et al 2009).

In the spinal cord, examinations of rat knee joint inflammatory pain and the selective use of opioid receptor antagonists have identified the specific opioid receptors through which the different types of TENS produce their action (Sluka et al 1999). The effects of HF-TENS were reduced with selective blockage of  $\delta$ -opioid receptors and the effects of LF-TENS reduced with blockage of  $\mu$ -opioid receptors (Sluka et al 1999). This finding has also been repeated in the rostral ventral medulla (RVM) indicating quite definite mechanisms of action for HF and LF-TENS (Kalra et al 2001).

Apart from acting on the opioid receptors in the spinal cord, LF-TENS has also been found to cause an increase in serotonin concentration (Sluka et al 2006). Again, using a model of inflammatory pain in the rat, LF but not HF-TENS stimulation resulted in an increase in serotonin concentration compared to sham TENS (Sluka et al 2006). Related to this finding, hypoalgesia with LF but not HF-TENS was reduced with blockage of serotonin receptors (5-HT<sub>2</sub> and 5-HT<sub>3</sub>) in the spinal cord (Radhakrishnan et al 2003). This reinforces the finding of Sluka et al (2006) and indicates clear differences in mechanisms of action between the two types of TENS in the spinal cord of rats. In addition to the differences in opioid receptors and the stimulation in release of serotonin in the spinal cord, HF-TENS has been found to increase the concentration of the neurotransmitter, gamma-Aminobutyric acid (GABA) in the spinal cord of rats (Maeda et al 2007). This increase in concentration was shown to occur with and without induced pain and only with HF-TENS simulation.

---

#### 4.5.2: Human Pain Models:

---

The mechanisms of hyperalgesia with TENS have also been investigated in human experimental pain models. Chesterton et al (2003) examined the effect of frequency,

intensity and stimulation site on pressure pain threshold. The authors examined six different parameter combinations of both LF- and HF-TENS on time taken to report pain threshold during treatment, and for 30 minutes post-treatment. The application of HF-TENS at high intensity, segmentally (at the site of pain) and in combination with an extrasegmental application (different limb) showed significant hypoalgesic effects during stimulation, and for 20 minutes post-stimulation (Chesterton et al 2003). This latent effect of intervention indicates involvement of supraspinal mechanisms as shown in the animal models.

In a series of related studies, Chen and Johnson (2010a; 2010b; 2011) investigated the effect of TENS frequency manipulation on different types of experimental pain (pressure, cold and ischaemic pain) in an effort to identify the most efficacious frequency of TENS stimulation. All studies employed repeated measure, crossover designs and adequate sample sizes in an effort to avoid the acknowledged limitations of previous research into TENS on experimental human pain (Chen et al 2008).

The first study in the series investigated the effects of HF-TENS (80Hz) and LF-TENS (3Hz) on Pressure Pain Threshold (PPT) in 32 healthy volunteers (Chen and Johnson 2010a). HF-TENS was found to more effectively prolong time taken to report PPT than LF-TENS. The authors discussed these findings and related the findings to segmental, spinal mechanisms. Unfortunately, as PPT was only measured during stimulation, no conclusions could be drawn regarding any latent effect of TENS. Also, in an effort to standardise the stimulation and examine the effects of frequency of stimulation, all other parameters except frequency of TENS were kept constant. This may have inadvertently resulted in a lack of effectiveness for LF-TENS, which is normally delivered at longer pulse widths and higher intensity.

The second published study employed the same study design and TENS stimulation on a model of cold-pressor pain (Chen and Johnson 2010b). As this experimental pain model allows pain to develop over time, pain threshold and pain intensity at 5 and 15 minutes was recorded as the outcome measures. Contrary to the first study, LF-TENS was found to be more efficacious, increasing time to pain threshold and pain intensity at 5 and 15 minutes. The authors suggest this finding may be due to LF-TENS increasing blood flow to the

periphery and thus warming the hand. This has, in previous studies, been associated with LF-TENS at intensities that generate phasic muscle contractions and thus a pump action for mobilising blood to the hand. In the current study, the intensity of LF-TENS was maintained below motor threshold and thus there should be no muscle activation to stimulate this warming effect. The authors state however, that as the participants controlled the intensity of the TENS, there may have been some muscle activation (Chen and Johnson 2010b).

In the final study of the series, the same study design was employed with the addition of a placebo TENS condition (Chen and Johnson 2011). The authors used the Submaximal Effort Tourniquet Test (SETT) to induce ischaemic pain in the upper limb of healthy volunteers and examined the effects of the three TENS conditions on pain intensity (VAS) at 1 and 2 minutes into pain and the Short-Form McGill Pain Questionnaire (SF-MPQ) one minute after release of pain. Similar to the first study on pressure pain, HF-TENS was found to reduce VAS scores of pain intensity compared to that achieved with LF-TENS. No differences were observed in the SF-MPQ measures of pain intensity. The reduction in pain intensity as measured by the VAS was suggested to be an effect of an increased rate of firing of afferent fibres with HF-TENS and thus changes to the concentration of neurotransmitter in the dorsal horn of the spinal cord (Chen and Johnson 2011). This however, was conjecture based on previous research on animal models of pain and the authors reinforce the need for further study on human models of pain to confirm mechanisms of action.

---

#### 4.5.3: Summary:

---

Overall, the current evidence for the neurophysiological mechanisms of TENS does not provide comprehensive explanations for the observed effects. Neurophysiological studies on animal models of pain have shown that LF-TENS activates  $\mu$ -opioid, 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors whilst HF-TENS acts through  $\delta$ -opioid receptors and increasing gamma-Aminobutyric acid (GABA) (Sluka et al 1998; Sluka et al 1999; Kalra et al 2001; Radhakrishnan et al 2003; Sluka et al 2005; Sluka et al 2006; Maeda et al 2007; DeSantana et al 2009). These mechanisms are yet to be confirmed in humans. Current research into the effects of TENS on experimental pain in humans has produced mixed results. This is mainly due to a myriad of study designs, outcome measures and TENS settings employed (Chen et

al 2008). Nevertheless, clinical pain syndromes are different from experimental pain. The different frequencies of TENS may have different effects on pain related to disease due to the individual and unique variations between patients.

#### 4.6: EVIDENCE FOR THE USE OF TENS FOR PAIN RELIEF:

---

TENS has not been tested as a method of pain relief for IC. Not only has TENS not been tested as an effective method of pain relief of IC, but also the potential for HF-TENS verses LF-TENS patterns of TENS to affect different portions of the IC pain experience has not been tested.

A review of the effects of TENS on IC pain is therefore impossible due to the lack of published studies. When searching with keywords “transcutaneous electrical nerve stimulation”, “transcutaneous nerve stimulation” and “intermittent claudication”, no studies are found that could be included in a review of TENS for IC pain. In an effort to establish whether TENS works for other painful conditions, a general ‘review of reviews’ was conducted to ascertain an overall view of the state of the literature.

Many of the early publications on TENS were either anecdotal or case reports and research on TENS did not involve RCTs (Sluka and Walsh 2003). Whether or not randomisation is employed has been demonstrated to affect the internal validity of research trials (Kunz and Oxman 1998). For example, 17/19 non-randomised studies excluded in a systematic review by Carroll et al (1996) indicated that TENS had a positive result on pain relief, whereas the randomised studies included in the review, indicated a negative effect of TENS on pain relief. Randomisation is employed to minimize overestimations of treatment effects making RCTs the ‘gold standard’ of studies that are seeking to answer a question regarding clinical efficacy (Schulz et al 1995).

Collections of RCTs are often synthesized into a systematic review, to provide a summary of data for a clinical question regarding efficacy. Sometimes the data from the studies in a systematic review are combined in a meta-analysis in an attempt to overcome the problem of reduced statistical power in studies with small sample sizes. Many studies produce

inconclusive findings due to having too few participants (Ottenbacher and Maas 1999). With these concerns in mind, the results of systematic reviews, meta-analyses and adequately powered RCTS are the focus of this section of the critical review.

The outcomes of systematic reviews and meta-analyses pertaining to the efficacy of TENS in various painful conditions are summarised in Table 4.1. This overview shows that all of the outcomes of these systematic reviews are inconclusive. The authors of the reviews explain that the reason for this is that many clinical trials are excluded from systematic reviews due to poor methodological quality. Hence, only a few methodologically robust studies may be available to analyse and draw conclusions. These reviews will be discussed in detail in an effort to summarise the key conclusions.

Table 4.1: Overview of recent reviews of the clinical efficacy of TENS

Reference	Clinical Condition	Number of Studies	Outcome
Carroll et al (2000)	Chronic Pain	19	Inconclusive
Brosseau et al (2003)	Rheumatoid Arthritis of the hand	3	Inconclusive
Nnoaham and Kumbang (2008)	Chronic Pain	25	Inconclusive
Khadilkar et al (2008)	Chronic Low Back Pain	4	Inconclusive
Rutjes et al (2009)	Osteoarthritis of the knee	13	Inconclusive
Walsh et al (2009)	Acute Pain	12	Inconclusive
Hurlow et al (2012)	Cancer Pain	3	Inconclusive

Carroll et al (2000) reviewed the effects of TENS on chronic pain. Included studies were limited to RCTs that compared TENS to control, sham TENS or other active TENS and utilised a subjective measure of pain intensity or relief. Chronic pain was defined as pain of at least 3 months duration and no limits were placed on sample size (Carroll et al 2000). Overall, 18 publications were included, covering nineteen RCTs as two RCTs were included within one publication. Meta-analysis was not possible due to heterogeneity of study designs. The findings of the review were conflicting with both positive and negative effects of TENS reported. The reason for the inconclusive results for TENS was mainly due to the heterogeneity of the studies included. The authors purposely employed broad inclusion

criteria in an effort to improve the number of studies to be evaluated. This tactic resulted in a wide range of conditions studied and a variety of methodological choices thus true synthesis and analysis was not possible. This issue of heterogeneity between studies relates back to the initial question of the review: to review the effects of TENS on chronic pain. As a population, chronic pain includes a diverse range of conditions and even within the same condition, no two patients will present with the same experience of pain (Melzack 2001). It is therefore not necessarily beneficial to attempt to summarise the effects of TENS in such a varied population and may be more useful to focus on a single chronic pain condition.

Brosseau et al (2003) chose to focus on just one chronic pain condition: Rheumatoid Arthritis (RA) in the hand. Again they limited their review to RCTs but also included Controlled Clinical Trials (CCTs). They included studies that used any type of TENS intervention in patients with diagnosed RA where the primary outcome measure was pain. Nine potential articles were found but only three met the inclusion criteria for the review. The outcome of the review was inconclusive. The reasons stated for this were again heterogeneity of methodologies in the included studies. All studies used slightly different applications of TENS and different methods to record any effects. The three included studies reported slightly different outcomes (Brosseau et al 2003): significant improvements in pain intensity compared to placebo (Abelson et al 1983); reduction in joint tenderness scores but not pain intensity (Langley et al 1984) and improvement in patient assessment of change in disease (Manheimer et al 1978). This review has addressed the limitations of that by Carroll et al (2000) by selecting a focussed question. This would have been ideal except they were again limited by the quantity and quality of the original literature.

Nnoaham and Kumbang (2008) updated the review of Carroll et al (2000). They used the same methodology for the review and included twenty-five studies in the final analysis. Despite adding six new RCTs to the body of evidence, no new conclusions were possible. Due to the same methodological heterogeneity, analysis of the effects of TENS on chronic pain was inconclusive. To gain a definitive answer, further original studies are required that address these methodological weaknesses, through the use of similar methods and measures.

Khadilkar et al (2008) chose a specific population but one with relatively large inherent variation: chronic Low Back Pain (LBP). Study inclusion criterion was RCT with more than 5 patients per treatment group. Chronic LBP was defined as pain lasting for more than 3 months, localised between the gluteal fold and the costal margin and in the absence of malignancy, fracture, infection, inflammatory disorder and neurological symptoms (Khadilkar et al 2008). They included all types of TENS intervention except percutaneous stimulation (via acupuncture needles) and only focussed on comparing TENS with sham TENS as a control in their analysis. They included more outcomes than have been selected in the previous reviews, specifically pain, back pain-related functional status, health status, work disability and patient satisfaction. After searching, 47 potential papers were identified, of which, four were included in the analysis. After analysis, the authors concluded that there was insufficient evidence of benefit of TENS compared to placebo TENS for all outcomes. TENS performed slightly better on some outcomes than others with more positive effects on pain intensity than back pain-related functional status or health status. This is a well-structured review of good quality studies. TENS again fails to show consistent effect. However, this could again be due to the population studied. In the studies reviewed, there was limited control of additional medication intake and applications of TENS varied amongst participants. Future research that examines the effects of TENS on sub-groups of chronic LBP utilising a pragmatic approach is required so that effects can be studied in relatively homogeneous populations.

Rutjes et al (2009) completed a review of electrical stimulation (interferential and TENS) for Osteoarthritis (OA) of the knee. In this review, the authors included both randomised, and quasi-randomised studies of patients with confirmed OA of the knee that used pain intensity as the main outcome. Sixteen trials were identified that met the inclusion criteria. Thirteen of these investigated the effects of TENS whereas the other examined either interferential stimulation or pulsed electrical stimulation (Rutjes et al 2009). There was enough similar data to conduct meta-analyses and after combining the data from all the studies (726 patients) the authors found a large standard mean difference (SMD) in pain intensity between TENS and control (-0.85, 95%CI-1.36 to -0.34) which relates to a reduction of 2.1

cm on a 10 cm Visual Analogue Scale (VAS) (Rutjes et al 2009). Despite this finding, the same problems were present in the data. Limitations in study size and lack of appropriately reported methodological quality and heterogeneity between studies limited the conclusions of the review. This is another example of a well-conducted review of a substantial amount of published literature that was unable to reach conclusions on the effects of TENS due to the heterogeneity of original studies.

Walsh et al (2009) conducted a review of TENS for acute pain, classified as pain lasting less than 12 weeks. Studies were included if they met the criteria as a RCT of patients with clinical pain excluding labour and dental pain. The main outcome measure was a standard subject pain scale (e.g. VAS) for either pain intensity or relief. Twelve studies were included in the review with 5 examining the effects of TENS on procedural pain and 7 including a range of pain states from haemophilia, strains and fractures to postpartum uterine contractions (Walsh et al 2009). Meta-analysis was not possible due to inadequate statistical tests and insufficient reporting. Overall, there were mixed results for TENS. Depending on the comparison, TENS was found to be as effective, or more effective than placebo TENS, no treatment or another active TENS condition. Nevertheless, no conclusions can be drawn due to the methodological inadequacies of the evidence and the heterogeneity of the population.

The most recent review of TENS (Hurlow et al 2012) examined the evidence base for TENS in cancer pain in adults and as before, they were unable to reach any conclusions except that large, multi-centre RCTs are required. The population investigated was patients with cancer-related pain, cancer treatment-related pain, or both over a 3-month period. The authors included RCTs that investigated the effects of TENS compared to either sham TENS or no-TENS control. Only three studies met the inclusion criteria with the main reason for exclusion being non-randomisation. Again, heterogeneity in the study methods did not permit meta-analysis and resulted in the inability to reach a conclusion.



---

#### 4.6.1: Summary:

---

The clinical efficacy of TENS remains largely inconclusive. Critical evaluation of the literature indicates that this may be due to heterogeneity, small sample sizes, lack of randomisation and in some cases the inadequacy of the stimulation parameters employed. When systematic reviews were able to conduct such analyses, results showed equal effectiveness between HF-TENS and LF-TENS at reducing pain and analgesic consumption (Osiri et al 2000; Bjordal et al 2003; Bjordal et al 2007; Johnson and Martinson 2007).

---

#### 4.7: CONCLUSION:

---

TENS is an established, non-pharmacological method of pain relief, employed with success in numerous clinical situations. There are two main 'types' of TENS that have been found to work through distinct neurophysiological mechanisms. Current reviews of the evidence do not conclusively support the hypoalgesic effects of TENS on clinical pain conditions. These reviews however are limited due to heterogeneity in the original study designs.

The possible hypoalgesic effects of TENS on IC pain have not been investigated. IC pain, similar to any chronic pain syndrome is a complex, multidimensional experience that is associated with psychosocial factors. This multifaceted nature of chronic pain conditions adds additional complexity to the investigation of novel analgesic interventions. Therefore, prior to clinical investigation, the effects of any novel analgesic intervention on experimentally induced pain are examined.

#### 4.8: CHAPTER 4 SUMMARY:

---

The aim of this chapter was to introduce the concept of TENS as a possible useful adjunctive intervention for lower limb ischaemic pain. TENS has been identified as a safe, non-pharmacological intervention for pain that is commonly used in clinical settings for relief from numerous painful conditions. Two main types of TENS stimulation have also been identified with distinct neurophysiological mechanisms of action in animal models of pain.

TENS has not been tested for IC pain and the clinical evidence for the efficacy of TENS on other painful conditions is limited. Systematic reviews of TENS have been unable to draw conclusions for the effects of TENS due to methodological limitations and heterogeneity within the original literature.

Due to the complex nature of clinical pain and thus the difficulties in evaluating outcomes in clinical trials, investigation of TENS on experimentally induced pain is warranted prior to investigating the effects of TENS on clinical IC pain. The next chapter will introduce the concept of experimental pain and discuss the current evidence for the effects of TENS on experimental pain similar to clinical IC pain.

## CHAPTER 5: LABORATORY-INDUCED ISCHAEMIC PAIN AND TENS

---

### 5.1: AIM OF CHAPTER 5:

---

Building on the discussion in the previous chapters, the aim of this chapter is to explore the concept of laboratory-induced pain as a possible method that could help address the two central aims of this thesis. Firstly, can laboratory-induced pain help with the investigation of the subjective descriptions of IC pain and secondly, can laboratory-induced pain help with the investigation of TENS as a possible adjunctive treatment for IC pain.

The benefits of experimental pain models will be discussed with a focus on laboratory-induced ischaemic pain (sections 5.2 and 5.3). The reported effects of TENS on this laboratory-induced ischaemic pain will be examined through a systematic review and the rationale for development of a laboratory-induced ischaemic pain method in the lower limb of a standing subject will be discussed (sections 5.4 and 5.5).

### 5.2: INVESTIGATING PAIN IN CLINICAL POPULATIONS AND LABORATORY-INDUCED PAIN:

---

Clinical pain syndromes are complex in nature, with both sensory-discriminative, affective-motivational and cognitive-evaluative components occurring simultaneously (Woolf 1979). These factors make patients with clinical pain syndromes less than ideal subjects for initial investigations into the efficacy of potential analgesics (Staahl and Drewes 2004). Clinically, patients often have confounding co-morbidities and are likely to be taking some form of medication (Staahl and Drewes 2004). Also, patients may interpret other effects of the intervention, e.g. effect on anxiety or depression relating to the disease, as a relief of pain.

Experimental pain models can be used to achieve a number of different goals: assessment of analgesic efficacy; studies of psychological variables and constructs involved in pain experience and report of this experience; evaluation of the underlying mechanisms of pain and pain control; measurement development and validation; as an adjunct to clinical pain assessment (Gracely 2006).

Experimental pain models are advantageous in pre-clinical investigation of an intervention as they allow some quantitative control over the input which subjects receive (Woolf 1979). The investigator can control the experimentally induced pain, i.e. the location, nature, intensity, frequency and duration, and provide quantitative measures of the psychophysical behavioural or the neurophysiological responses (Graven-Nielsen et al 2001; Staahl and Drewes 2004).

There are two main limitations of using experimentally induced pain to test interventions. Firstly, the attempt to artificially separate the components of the pain experience, i.e. separating the physiological nociceptive mechanisms from pain affect, causes oversimplification of the sensation to the point where it becomes unlike clinical pain (Woolf 1979). Secondly, experimental studies are unable to reproduce the physiological features and the accompanying psychological qualities of clinical pain in the laboratory (Gracely 2006).

Despite these reported limitations, experimentally induced pain allows the researcher the opportunity to obtain reproducible results in test-retest experiments in controlled conditions thus making them ideal for the testing of interventions (Handwerker and Kobal 1993).

### 5.3: A PRE-CLINICAL MODEL OF IC PAIN:

---

There are a number of experimental pain models currently in use, including heat, cold, ischaemic, mechanical pressure, electrical and chemical. The ischaemic pain model, which induces ischaemic muscle pain, is the method of interest in this thesis as this seems to most closely reflect IC pain.

The ischaemic model involves arresting blood flow to a limb using a tourniquet and exercising the muscles distal to the tourniquet to induce ischaemic pain (Graven-Nielsen et al 2003; Staahl and Drewes 2004). This experimental pain model can be viewed as having some physiological similarities to IC, where the atherosclerotic process in the arteries limits

blood flow to the limb(s), creating an ischaemic environment. What is not known however, is whether the pain experiences are comparable.

Lewis (1932) first proposed induction of pain by muscle ischaemia. Generally, a pneumatic tourniquet is applied, and after a period of voluntary muscle contractions, distal to the tourniquet, an unpleasant tonic pain sensation develops (Graven-Nielsen et al 2001). The number and level of force of the contractions are important determinants for the resulting pain. It is thought that these aspects determine the build-up of lactate. Lactate is a by-product of ischaemic contraction or more specifically, anaerobic metabolism is thought to be the main contributor to the pain induced by excitation of nociceptive C-fibres (Pertovaara et al 1984; Graven-Nielsen et al 2001).

A standardised method of reliably inducing ischaemic pain in human subjects was developed by Smith et al (1966) and termed the 'Submaximal Effort Tourniquet Technique' (SETT). Ischaemic pain was induced in the arm of 15 healthy volunteers to examine the effects of intravenous morphine injections. This technique has been developed and adapted over time by a number of different authors (see Table 5.1) (Moore et al 1979; Woolf 1979; Rosenblatt and Hetherington 1981; Pertovaara et al 1984; Posner 1984; Roche et al 1984; Roche and Gijssbers 1986; Walsh et al 1995a; Foster et al 1996; Benedetti 1996; Amanzio and Benedetti 1999; Roche et al 2002; Johnson and Tabasam 2003).

---

#### 5.3.1: Variations of the SETT:

---

Although the SETT is a standardised method different investigators have employed different parameters. There are seven main parameters that can be modified: limb, subject position, desanguination, cuff position, cuff width, exercise load and exercise repetitions. A review of published studies which have used the SETT demonstrates variations in the methodologies employed (Table 5.1 and summarised in Table 5.2).

As previously discussed, laboratory-induced ischaemic pain is hypothesised to be mediated by an increase in metabolites. Thus, seemingly minor changes in the force of contraction and the number of repetitions have the potential to drastically affect a participant's rating

of pain (Pertovaara et al 1984). Despite the multitude of variations in SETT methodologies, ischaemic pain was successfully induced in all of the studies.

Table 5.1: Published studies that employed the SETT procedure to induce ischaemic pain (continued on next 4 pages)

<b>Authors</b>	<b>Smith et al (1966)</b>	<b>Moore et al (1979)</b>	<b>Woolf (1979)</b>
<b>Participants</b>	45 males	2 males 3 females	80 males
<b>Limb</b>	ND UL	ND UL	L UL
<b>Participant Position</b>	Supine	Sitting	Not stated
<b>Desanguination</b>	Vertical	Vertical	Vertical
<b>Compression</b>	Esmarch bandage applied	Esmarch bandage applied	No compression
<b>Desanguination Time</b>	Not specified	Not specified	60 seconds
<b>Cuff Position</b>	Upper arm	Upper arm	Forearm
<b>Cuff Pressure (mmHg)</b>	250	200	250
<b>Cuff Width</b>	3 inches	Not stated	7.5 cm
<b>Exercise</b>	Hand grips	Handgrips	Handgrips
<b>Exercise Reps</b>	20	20	20
<b>Exercises Load</b>	7.72 kg	50% or 30% MVC	2.5 kg
<b>Exercises Time</b>	2s hold/2s relax	2 s hold/ 2s relax or no hold (every 4s)	2s / 2s Started 20s after inflation
<b>Start Point (Time 0)</b>	Cessation of exercises	Cuff inflation	End of exercises
<b>End Point</b>	Pain tolerance 3.3–53 mins (19 median)	Pain tolerance or 20 minutes	Pain tolerance
<b>Outcome measures</b>	5 point likert scale at irregular intervals:	0-100 NRS at random intervals	VAS at 1 min intervals
<b>Important Results</b>	Induced a reliable and comparable level of pain	50% MVC and 2 second hold reported to be best	TENS reduced intensity and increased endurance to pain

Table 5.1 (continued): Published studies that employed the SETT procedure to induce ischaemic pain

<b>Authors</b>	<b>Rosenblatt and Hetherington (1981)</b>	<b>Posner (1984)</b>	<b>Pertovaara et al (1984)</b>
<b>Participants</b>	8 males 2 females	6 males 6 females	9 males 8 females
<b>Limb</b>	Not specified	D UL	UL
<b>Participant Position</b>	Not stated	Sitting	Not stated
<b>Desanguination</b>	Vertical	Vertical	Vertical
<b>Compression</b>	Elastic bandage	Inflatable sleeve	Not stated
<b>Desanguination Time</b>	Not specified	Not stated	60 seconds
<b>Cuff Position</b>	Upper Arm	Upper arm	Upper arm
<b>Cuff Pressure (mmHg)</b>	250	250	200, 250 and 300
<b>Cuff Width</b>	Not stated	Not stated	14 cm
<b>Exercise</b>	Handgrips	Handgrips	Handgrips
<b>Exercise Reps</b>	20	Not stated	15 or 30
<b>Exercises Load</b>	30lb	50% MVC	70% MVC
<b>Exercises Time</b>	20 within 1 minute	2.5s hold/relax for 1 min	2s hold/relax
<b>Start Point (Time 0)</b>	Cuff inflation	Not stated	Cessation of exercises
<b>End Point</b>	Pain tolerance	Pain tolerance	15 mins
<b>Outcome measures</b>	Time to pain tolerance VAS post pain tolerance	VAS continuous	VAS of ischaemic and pressure pain
<b>Important Results</b>	No difference in time to pain tolerance or in reported pain intensity with single or dual channel TENS vs. control	SETT can be used to detect small changes in pain intensity with hypoalgesic intervention	Higher ischaemic pain = lower pressure pain



Table 5.1 (continued): Published studies that employed the SETT procedure to induce ischaemic pain

<b>Authors</b>	<b>Roche et al (1984)</b>	<b>Roche and Gijsbers (1986)</b>
<b>Participants</b>	24 males 24 females	11 males 12 females
<b>Limb</b>	L UL	L UL
<b>Position</b>	Sitting	Sitting
<b>Desanguination</b>	Not stated	Not stated
<b>Compression</b>	Not stated	Not stated
<b>Desanguination Time</b>	Not stated	Not stated
<b>Cuff Position</b>	Upper arm	Upper arm
<b>Cuff Pressure (mmHg)</b>	250	250
<b>Cuff Width</b>	12 cm	12 cm
<b>Exercise</b>	Handgrips	Handgrips
<b>Exercise Reps</b>	20	20
<b>Exercises Load</b>	25% MVC	25% MVC
<b>Exercises Time</b>	2s hold/relax	2s hold/relax
<b>Start Point (Time 0)</b>	Cessation of exercises	Cessation of exercises
<b>End Point</b>	25 mins or pain tolerance	25 mins or pain tolerance
<b>Outcome measures</b>	Pain threshold Pain tolerance VAS and PPI every minute MPQ at tolerance	MPQ at tolerance and 7 days later
<b>Important Results</b>	Time to threshold and tolerance increased with LF, low intensity TENS Time to tolerance and endurance increased with HF, high intensity TENS	Memory of one-off ischaemic pain more effective than for Rheumatoid pain

Table 5.1 (continued): Published studies that employed the SETT procedure to induce ischaemic pain

<b>Authors</b>	<b>Walsh et al (1995a)</b>	<b>Foster et al (1996)</b>	<b>Benedetti (1996)</b>
<b>Participants</b>	32 females	24 males 24 females	154 males 186 females
<b>Limb</b>	ND UL	UL	UL
<b>Position</b>	Sitting	Sitting	Supine
<b>Desanguination</b>	Vertical	Vertical	Vertical
<b>Compression</b>	7 cm wide bandage applied	Elastic bandage	Esmarch bandage
<b>Desanguination Time</b>	60 seconds	60 seconds	Not stated
<b>Cuff Position</b>	Upper arm	Upper arm	Upper arm
<b>Cuff Pressure (mmHg)</b>	200	200	250
<b>Cuff Width</b>	Not Stated	13 cm	Not stated
<b>Exercise</b>	Handgrips	Handgrips	Handgrips
<b>Exercise Reps</b>	20	20	12
<b>Exercises Load</b>	75% MVC	75% MVC	7.2 kg
<b>Exercises Time</b>	1s holds Completed in 1 min	2s/1s hold/relax	2s/2s hold/relax
<b>Start Point (Time 0)</b>	Cuff inflation	Cuff inflation	Score of 7 on NRS
<b>End Point</b>	10 minutes (Deflated over 2 mins)	10 minutes (Deflated over 2 mins)	Pain tolerance
<b>Outcome measures</b>	VAS every minute (0-12)	VAS every minute	0-10 NRS Pain tolerance
<b>Important Results</b>	Mean VAS decreased with LF-TENS compared to control and HF-TENS VAS from minutes 7-9 decreased with LF-TENS compared to all other groups	No difference in VAS or MPQ scores between groups or over time	The SETT is a useful tool with which to study the placebo response

Table 5.1 (continued): Published studies that employed the SETT procedure to induce ischaemic pain

<b>Authors</b>	<b>Amanzio and Benedetti (1999)</b>	<b>Roche et al (2002)</b>	<b>Johnson and Tabasam (2003)</b>
<b>Participants</b>	132 males 97 females	6 males 6 females	18 male 12 female
<b>Limb</b>	UL	L UL	UL
<b>Position</b>	Supine	Sitting	Not stated
<b>Desanguination</b>	Vertical	Not stated	Vertical
<b>Compression</b>	Esmarch bandage	Not stated	Not stated
<b>Desanguination Time</b>	Not stated	Not stated	1 min
<b>Cuff Position</b>	Upper arm	Upper arm	Forearm
<b>Cuff Pressure (mmHg)</b>	300	250	200
<b>Cuff Width</b>	Not stated	12 cm	15 cm
<b>Exercise</b>	Handgrips	Handgrips	Handgrips
<b>Exercise Reps</b>	12	20	20
<b>Exercises Load</b>	6.5 kg	25% MVC	75%
<b>Exercises Time</b>	2s/2s hold/relax	2s hold/relax	2s hold/relax
<b>Start Point (Time 0)</b>	Cessation of exercises	End of exercises	Cuff inflation
<b>End Point</b>	Pain tolerance	12 mins	12 mins
<b>Outcome measures</b>	Pain tolerance	Pain threshold Pain tolerance VAS at minutes 3,6,9 and 12	VAS every minute MPQ post-test
<b>Important Results</b>	The expectation placebo response is driven by opioid system conditioning is not	Placebo TENS and interferential increased time to pain threshold and tolerance	No difference in VAS or SF-MPQ scores between groups- TENS vs. control, placebo and IFC

Table 5.2: Summary of variations in SETT methods employed in published studies

Parameter	Study Variations
<b>Limb</b>	All studies use the upper limb (UL) whether it is the dominant (D) or non-dominant (ND).
<b>Position</b>	All studies also have the participants supine or sitting with the arm resting on a table.
<b>Desanguination</b>	Desanguination of the limb is slightly different and not stated in a number of the studies.
<b>Cuff Position</b>	The cuff is positioned commonly on the upper arm with two exceptions where it is positioned on the forearm (Woolf 1979; Johnson and Tabasam 2003).
<b>Cuff Width</b>	When reported, the cuff widths use varied from 7.5cm (Woolf 1979) to 14cm (Pertovaara et al 1984).
<b>Exercise Load</b>	Most studies calculated the participants' Maximum Voluntary Contraction (MVC) but the force and number of contractions performed varied considerably. The exercise load used, ranged from 25% MVC (Roche et al 1984; Roche and Gijssbers 1986), to 75% MVC (Johnson and Tabasam 2003; Foster et al 1996; Walsh et al 1995a). In contrast, a number of studies used a standardised grip tension, ranging from 2.5kg to 7.72kg rather than a percentage of MVC (Smith et al 1966; Woolf 1979; Rosenblatt and Hetherington 1981; Benedetti 1996; Amanzio and Benedetti 1999).
<b>Exercise Repetitions</b>	The number of exercise repetitions ranged from 12 (Benedetti 1996; Amanzio and Benedetti 1999) to 30 (Pertovaara et al 1984) with the majority using 20 repetitions.

#### 5.4: TENS AND LABORATORY-INDUCED ISCHAEMIC PAIN:

---

TENS has been shown to be effective for some clinical pain syndromes. However, it has not been tested for IC pain. Prior to investigation of a novel analgesic technique on clinical pain, laboratory testing in healthy volunteers is advocated (Staahl and Drewes 2004; Gracely 2006).

TENS has been trialled on ischaemic pain in healthy volunteers. Reviews of these studies have found mixed evidence for the efficacy of TENS for ischaemic pain (Walsh 1997; Claydon et al 2011). These reviews however are either out of date (Walsh 1997) or their focus is not ischaemic pain (Claydon et al 2011). An updated, comprehensive review is indicated that focuses solely on the effects of TENS on experimentally induced ischaemic pain.

---

##### 5.4.1: Systematic Review of TENS for Ischaemic Pain in Healthy Volunteers:

---

This next section will describe a systematic review conducted to evaluate the current evidence for the hypoalgesic effects of TENS on experimentally induced ischaemic pain on healthy volunteers.

##### 5.4.1.1: Methodological Considerations:

---

To be able to evaluate and establish the hypoalgesic efficacy of TENS for ischaemic pain, methodologically robust trials are required. The essential components of study design that help to ensure methodological rigour will now be briefly considered.

Randomisation and blinding have been shown to affect the internal validity of research studies (Schulz et al 1995; Kunz and Oxman 1998). By randomising group allocation, participant characteristics and confounding variables will be more likely to be distributed equally between the groups (WHO 2005). These variables may include baseline values of outcome measures or general participant characteristics. In non-randomised trials, bias is often evident and the direction and extent of this bias is often impossible to predict (Kunz and Oxman 1998). Randomisation is therefore an essential aspect of trial design when trying to avoid or minimise this type of bias. Another form of bias common in research trials is measurement bias. Measurement bias can be minimised by using sufficient blinding of

participants and researchers. If participants or researchers involved in providing or measuring the outcomes of a study are not blind to group or treatment allocation they may respond differently and thus consciously or subconsciously affect the measurement of outcomes (Sim and Wright 2000). Without double blinding of both the researcher and the participant, treatment effects can be overestimated by an average of 17% (Schulz et al 1995). Blinding and randomisation are therefore two key aspects of trial design without which, treatment effects may be inflated and bias introduced into the outcomes.

#### 5.4.1.2: Search Strategy:

---

The electronic databases Scopus, AMED, CINAHL, MEDLINE and Science Direct were searched for relevant Randomised Controlled Trials (RCTs) published in English within the period from 1960-2011. The search terms used and combinations for these databases are detailed in Table 5.3 and full details of the search strategy and articles excluded are presented in Appendix 1. Hand searches of reference lists were also conducted to reduce the chance of missing any pertinent studies.

Table 5.3: Details of the search strategy employed in this systematic review.

Database	Field	Keywords	Combinations	Results
Scopus	Full Text	1. Transcutaneous electrical nerve stimulation	(1 OR 2) AND 3	175
		2. TENS	(4 OR 5) AND 3	
		3. Isch*mic pain	6 AND 3	
		4. Transcutaneous Nerve Stimulation		
		5. TNS		
		6. Electrical Stimulation		
AMED, CINAHL and MEDLINE	Full Text	1. Transcutaneous electrical nerve stimulation	(1 OR 2) AND 3	19
		2. TENS	(4 OR 5) AND 3	
		3. Isch*mic pain	6 AND 3	
		4. Transcutaneous Nerve Stimulation		
		5. TNS		
		6. Electrical Stimulation		
Web of Knowledge	Full Text	1. Transcutaneous electrical nerve stimulation	(1 OR 2) AND 3	25
		2. TENS	(4 OR 5) AND 3	
		3. Isch*mic pain	6 AND 3	
		4. Transcutaneous Nerve Stimulation		
		5. TNS		
		6. Electrical Stimulation		

#### 5.4.1.3: Inclusion Criteria and Methodological Assessment:

To be included in the review, studies had to be:

- Randomised Controlled Trials
- Conducted on healthy human volunteers
- Used an induced ischaemic pain model
- Compared TENS to Placebo and/or Control
- Used pain as the primary outcome measure

Standardised data extraction tables were used to summarise the data from each study (Appendix 1) and a modified Jadad Scale (Claydon et al 2011) (Appendix 3) was used to evaluate the quality of each study (Jadad et al 1996). This methodological rating scale was chosen because it addresses randomisation and blinding which have been established as

factors that affect the internal validity of trials (Schulz et al 1995; Kunz and Oxman 1998). The Jadad scale was used to categorise trials into high and low quality. A study was deemed to be high quality if it scored 3 or more points (out of 5) and low quality if it scored 2 or fewer (Claydon et al 2011).

#### 5.4.1.4: Data Analysis:

---

The studies included in the review are reported using descriptive analysis and qualitative review. Due to methodological differences further quantitative analysis was not possible.

#### 5.4.1.5: Results:

---

Figure 5.1 details the outcomes of the search strategy. Six RCTs were included in the final review. All studies employed a version of the SETT to the upper limb of healthy volunteers. Various study designs and variations of the SETT were employed along with different TENS stimulation parameters. Details of the full texts reviewed and reasons for exclusion are displayed in Table 5.4.

#### Methodological Quality:

---

Study quality of the research included in the review ranged from scores of 1-5 on the modified Jadad scale (Table 5.5). Three studies were classified as high quality (Walsh et al 1995a; Foster et al 1996 and Chen and Johnson 2011), with Chen and Johnson (2011) scoring the maximum of 5 points. All studies performed randomisation of some kind although only two described their methods (Roche et al 1984; Chen and Johnson 2011). The three high quality studies also managed to perform double blinding of the researcher and participant (Walsh et al 1995a; Foster et al 1996; Chen and Johnson 2011). The other studies were either single-blinded (Johnson and Tabasam 2003) or no blinding was reported at all (Rosenblatt and Hetherington 1981; Roche et al 1984). In terms of statistical power, all studies were underpowered except Chen and Johnson (2011) who achieved the required 26 participants per group (see Appendix 2 for the details of the power calculation).



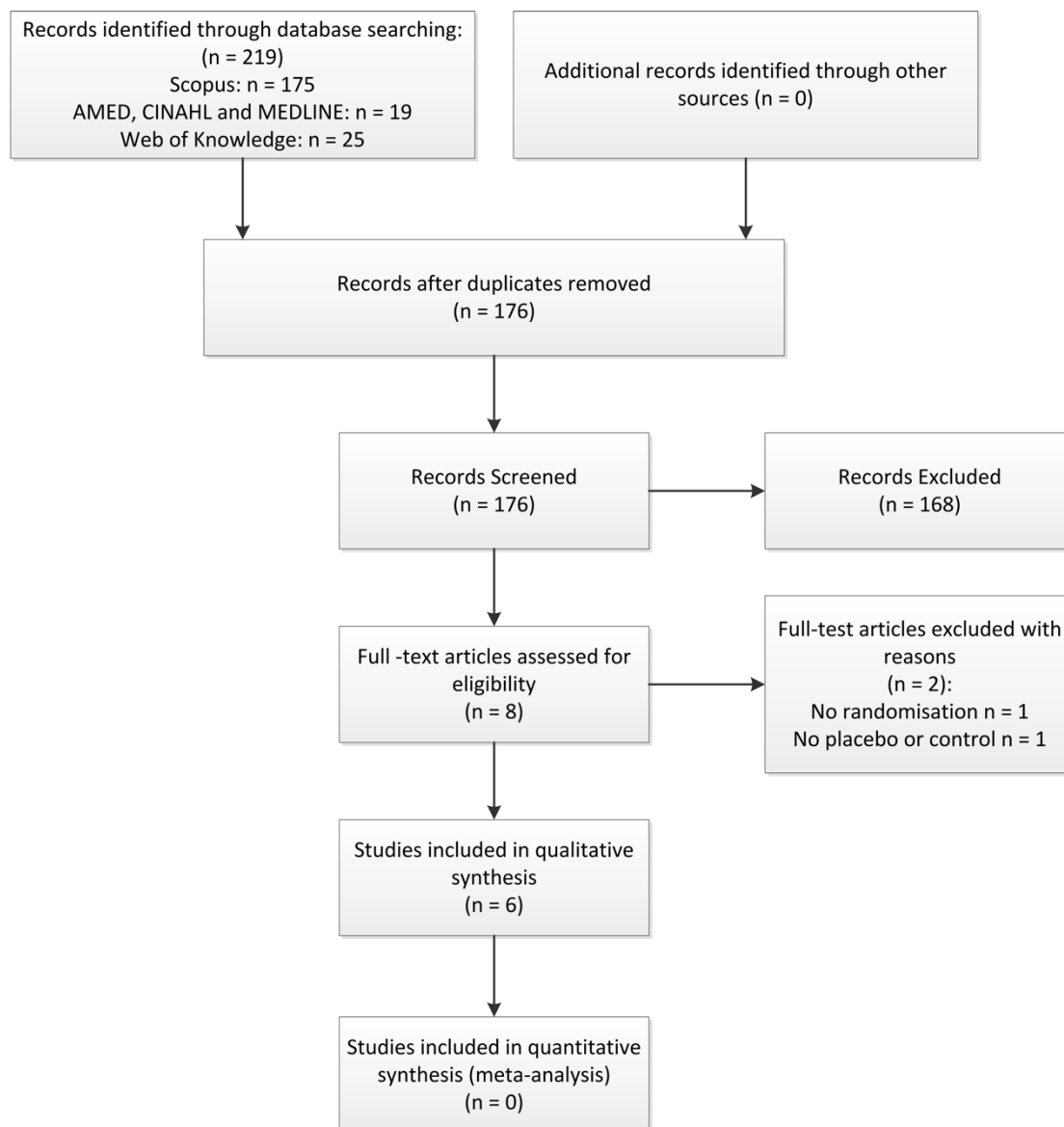


Figure 5.1: PRISMA diagram detailing the outcome of the search strategy. Details of studies screened and reasons for exclusion are detailed in Appendix 1 and Table 5.4.

Table 5.4: Full-text articles screened and reasons if excluded from final review

<b>Author:</b>	<b>Year:</b>	<b>Reason for Exclusion:</b>
Woolf	1979	No randomisation
Rosenblatt and Hetherington	1981	
Roche et al	1984	
Walsh et al	1995a	
Foster et al	1996	
Johnson and Tabasam	2003	
Brown et al	2007	No placebo or control
Chen and Johnson	2011	

Table 5.5: Articles included in the review and scores for methodological quality related to the modified Jadad scale (Appendix 3).

<b>Study</b>	<b>Randomisation</b>		<b>Blinding</b>		<b>Statistical Power</b>	<b>Score</b>	<b>Quality</b>	<b>General Outcome</b>
	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>			
Rosenblatt and Hetherington 1981	Yes	No	No	No	No	1	Low	Negative
Roche et al 1984	Yes	Yes	No	No	No	2	Low	Positive
Walsh et al 1995a	Yes	No	Yes	Yes	No	3	High	Positive
Foster et al 1996	Yes	No	Yes	Yes	No	3	High	Negative
Johnson and Tasbasam 2003	Yes	No	No	No	No	1	Low	Negative
Chen and Johnson 2011	Yes	Yes	Yes	Yes	Yes	5	High	Positive

### General Outcomes:

---

Table 5.5 also provides the general outcomes for each study included in the review. Two of the high quality studies (Walsh et al 1995a; Chen and Johnson 2011) reported positive results for the effects of TENS on ischaemic pain along with Roche et al (1984). The other three reported no difference between TENS and either placebo or control conditions (Rosenblatt and Hetherington 1981; Foster et al 1996; Johnson and Tabasam 2003). There appears to be a slight trend towards positive outcomes in high quality studies.

### Comparison Against Control/Placebo/Sham:

---

As the application of electro-physical modalities has been shown to be associated with significant placebo effects a placebo, or sham, intervention is essential to any study of the effects of TENS (Johnson and Bjordal 2011). It is important therefore, to examine the control conditions employed in the studies under review.

The two earliest studies examined the effects of TENS compared to a no-TENS control (Rosenblatt and Hetherington 1981; Roche et al 1984). The control condition consisted of the same SETT procedure with no intervention. These studies also did not report any blinding procedures, both methodological choices that can lead to overestimation of treatment effects (Schulz et al 1995). Rosenblatt and Hetherington (1981) reported no difference in time to pain tolerance or reduction in pain intensity with TENS but Roche et al (1984) observed an increase in time to pain threshold and tolerance with LF/LI-TENS and an increase in time to pain tolerance and endurance with HF/HI TENS. The positive results reported by Roche et al (1984) are thus questionable and maybe if compared with a placebo control, would not be evident.

The other studies included in this review employed both a placebo intervention and a control condition. The placebo conditions were reported as being identical to the active conditions although no current reached the participant. The participant is informed that the dosage of the intervention is at sub-threshold levels and they may, or may not perceive any stimulation. Walsh et al (1995a) even encouraged participants to alter the stimulation intensity similar to the other experimental conditions so that the experience was as similar

as possible without the application of current. The success of participant belief in placebo was reported by Walsh et al (1995a) and Foster et al (1996) mentioning the “several subject in the placebo group reported to have experienced sensations beneath the electrodes” (Foster et al 1996, p302). Of the studies that compared TENS to both placebo and control conditions, two of the high quality trials reported positive effects of TENS compared to placebo for pain intensity as measured by a VAS (Walsh et al 1995a; Chen and Johnson 2011) and the sensory component of the SF-MPQ (Chen and Johnson 2011). The other high quality trial found no differences between all groups (Foster et al 1996). Johnson and Tabasam (2003) also reported no change in VAS or SF-MPQ with TENS compared to placebo or control. The fact that two of the high quality studies reporting positive effects of TENS do so compared to placebo, increases the importance of the findings. The negative findings in the other studies will be explored further in the section relating to stimulation parameters.

#### Methodological Differences and Outcomes:

Despite all studies meeting the inclusion criteria, they all employed slightly different methodologies to assess the effects of TENS on induced ischaemic pain. All studies used a version of the SETT as devised by Smith et al (1966) and all tested one, or both of the most common types of TENS (HF or LF-TENS) (Table 5.6). Nevertheless, the actual parameters of the SETT and TENS employed differed between the studies.

#### **SETT METHOD**

Four of the six studies followed the method described by Smith et al (1966) and applied a tourniquet to the upper arm to induce ischaemic pain (Rosenblatt and Hetherington 1981; Roche et al 1984; Walsh et al 1995a; Foster et al 1996). The two most recent studies from the same centre however, applied the tourniquet to the forearm to induce ischaemia (Johnson and Tabasam 2003; Chen and Johnson 2011). The reasons for this methodological change are well explained however; this fundamental change to the induction of ischaemia may have affected the pain participants experienced and thus the hypoalgesic effects of TENS. The authors report that the “pain intensity ratings were similar to those previously reported by other groups using the same technique” (Johnson and Tabasam 2003, p 214), which is fair but the quality and nature of the development of induced pain is not described.

This is a crucial point of interest for the current study that aims to examine the relationships between TENS and the development of ischaemic pain.

The most common cuff pressure used was 200mmHg (4/6 trials) with the older studies using 250mmHg (Rosenblatt and Hetherington 1981; Roche et al 1984). The exercise used within the SETT procedure to induce ischaemic pain is hand gripping against a specified force. Most studies asked participants to complete 20 of these exercises (5/6) with Chen and Johnson (2011) selecting 15 instead. Seventy-five percent of participants' maximum grip strength was the most popular force (4/6) again with the older studies using either 30lb for all participants (Rosenblatt and Hetherington 1981) or maximum grip strength (Roche et al 1984). Both cuff pressure and degree of exercise has been shown to be positively related to intensity of pain produced by the SETT (Pertovaara 1984). As the studies of Rosenblatt and Hetherington (1981) and Roche et al (1984) employed both increased cuff pressure and an increase level of exercise it could be concluded that participants in these studies experienced greater intensity of pain. Mean time to pain tolerance in these two studies is comparable: 9.7 minutes for Rosenblatt and Hetherington (1981) and 10.8 minutes for Roche et al (1984). All other studies limited the time for the SETT and thus did not report time to tolerance.

Another important difference in the methods of pain induction was that of SETT duration. Rosenblatt and Hetherington (1981) and Roche et al (1984) both used 25 minutes as the maximum time whereas the other studies used 12 minutes (Walsh et al 1995a; Foster et al 1996), 10 minutes (Johnson and Tabasam 2003) or 2 minutes (Chen and Johnson 2011). The benefit of the longer duration of pain is that the effects of TENS can be examined over a prolonged period and thus the effects on different aspects of the pain experience investigated (i.e. pain threshold, tolerance, endurance, intensity and quality). Important to note however, is that despite the 25 minutes allowed in the studies by Rosenblatt and Hetherington (1981) and Roche et al (1984), mean time taken to report pain tolerance was approximately 10 minutes. Therefore the 10-12minutes employed by three of the other studies should be sufficient to allow examination of the complete pain experience (Walsh et al 1995a; Foster et al 1996; Johnson and Tabasam 2003). The study design of Chen and

Johnson (2011) was slightly different, requiring each participant to complete three consecutive inductions of pain in one session. From an ethical perspective, the shortened period of pain is understandable in this design as it would be unreasonable to expect participants to complete consecutive, prolonged experiences to ischaemia. Nevertheless, the results must be interpreted in this context and any conclusions only apply to the initial experiences of ischaemic pain (i.e. threshold levels).

#### PAIN MEASUREMENT

All studies employed a measure of pain intensity upon which the effects of TENS was evaluated. Rosenblatt and Hetherington (1981) measured time taken to report pain tolerance and Roche et al (1984) recorded time to pain threshold and pain endurance. All studies employed a Visual Analogue Scale (VAS) to measure pain intensity at different time points. Most commonly, a VAS was conducted every minute during pain induction and at the end of cuff deflation to measure 'current pain intensity level'. Roche et al (1984) used the Present Pain Intensity (PPI) of the MPQ but all others employed a 10cm line with anchors relating to 'no pain; and 'worst pain imaginable' (Walsh et al 1995a; Foster et al 1996; Johnson and Tabasam 2003; Chen and Johnson 2011). Rosenblatt and Hetherington (1981) only recorded one VAS measurement, immediately after deflation of the cuff.

All studies with the exception of Rosenblatt and Hetherington (1981) also used a version of the McGill Pain Questionnaire (MPQ). Participants were asked to complete the questionnaire at the end of the SETT procedure in relation to the 'worst pain experienced'. Roche et al (1984) and Foster et al (1996) used the full version whereas the other three studies asked participants to complete the Short-Form MPQ (Walsh et al 1995a; Johnson and Tabasam 2003; Chen and Johnson 2011).

#### TENS PARAMETERS

There are not definitive agreed stimulation parameters for HF and LF-TENS. It is generally agreed that HF-TENS consists of frequency between 50 and 100Hz, pulse duration of between 50 and 200µsec and intensity set to participant evaluation of a 'strong, but comfortable' sensation (Charlton 2005). LF-TENS is classified as a frequency between 2 and

4Hz, pulse duration 100-400µsec and intensity of 'tolerance threshold' (as high as the participant can tolerate) (Charlton 2005). In addition, electrode placement has been shown to be an important variable relating to the hypoalgesic effects of TENS (Chesterton et al 2003; Brown et al 2007). Again, only general recommendations exist where HF-TENS is to be applied over the painful region and LF-TENS at either acupuncture points, trigger points or over the painful region (Charlton 2005). The final characteristic that is important for the dosing and efficacy of TENS is timing (Walsh et al 1995b). TENS is thought to elicit immediate and latent hypoalgesic effects (Johnson 1991). Therefore the relationship between the time TENS stimulation begins and the time that pain experience begins is key to the effects observed. This relationship and the specific effects of TENS have not been conclusively established although both HF and LF-TENS are recommended to be switch on for 30 minutes (Charlton 2005).

Most of the studies in the review adhered to these settings. However as most of the studies included in the review aimed to test the efficacy of different stimulation parameters of TENS, between-study variation is common (Table 5.6). With this in mind, rather than attempting to generalise across the studies, each application of TENS will be discussed in turn and then general points synthesised within the discussion.

Rosenblatt and Hetherington (1981) aimed to investigate the ability of single, or dual channel TENS to alleviate ischaemic pain. The authors reported that no changes were observed in time to report pain tolerance or in VAS scores. They used HF-TENS with a frequency of 100Hz, pulse duration of 40µsec; intensity determined as 'maximum tolerated intensity' and applied either through 2 (single), or 4 (dual) electrodes just proximal to the cuff (Table 5.6). These stimulation settings do not fit into the recommended settings for HF-TENS. The frequency is appropriate although the pulse duration is too short, stimulation intensity too high and electrodes are not placed over the region of pain. In addition, TENS stimulation was turned on only just before the start of the SETT. This choice would have been sufficient if the participants had continued with the SETT for the whole 25 minutes (close to the recommended 30 minutes). However as mentioned previously, participants reached tolerance in a mean time of 9.7 minutes (Rosenblatt and Hetherington 1981). This

means that, on average, participants were not receiving the recommended dose of TENS stimulation. The negative finding for TENS may therefore be a result of the insufficient application of TENS rather than no evidence of effect.

Roche et al (1984) set out with the aim of recording the differences in response of healthy subjects to ischaemic pain when treated with TENS. LF/LI-TENS was found to increase time to pain threshold and tolerance and HF/HI-TENS was found to increase time to pain tolerance and increase the endurance of pain. In this low quality, non-blinded study, three dosages of TENS were investigated (see Table 5.6). The authors attempted to investigate different combinations of frequency and intensity, with one HI HF-TENS condition and two LF-TENS conditions (one with LI and one with HI). The HF-TENS condition settings are detailed in Table 5.6 and again they do not fit with the recommended dosage. The frequency is within the correct range but the pulse duration was too long (1000µsec) and intensity too strong. However, the electrode placement and duration of stimulation were appropriate. For the LF-TENS conditions, the frequency and electrode placement were suitable but the pulse duration was again too long (100,000µsec). The design aimed to investigate the effects of different stimulation intensities. Therefore the 'barely perceptible' intensity used for the LF/LI-TENS group is understandable. The study was generally low in quality with no blinding of researcher, no repeated measures and limited statistical testing as there was no attempt to quantify any baseline differences between groups that could have accounted for the results observed.

Walsh et al (1995a) conducted a high quality, double-blind investigation that aimed to compare the effects of HF and LF-TENS on induced ischaemic pain. Overall, the researchers found that LF-TENS reduced mean pain intensity compared to HF-TENS and control and this was especially evident from minutes 7-9 where VAS scores were decreased in the LF-TENS group compared to HF-TENS and placebo. The TENS setting used for the two interventions are detailed in Table 5.6. The parameters chosen align with the current guidance, except for the pulse duration for HF-TENS (>200µsec) and the intensity of LF-TENS (not maximum tolerated). A significant positive however, was the fact that the researchers encouraged participants to control and alter the intensity of stimulation, something which has been



shown to increase the hypoalgesic effects of TENS (Pantaleão et al 2011). Nevertheless, as the authors' aim was to compare HF against LF-TENS, the decision to maintain the other parameters at equal levels strengthens any conclusions regarding the effects of frequency. The only point of criticism of this study is the experimental design. There was no randomisation of entry into the condition i.e. all participants completed intervention condition second. By always completing the intervention condition second, regardless if it is control, placebo or TENS, there is the possibility of a fear, training, or familiarisation effect (Shanahan et al 2006). If participants have a bad experience, they could be more fearful and thus there is an increased chance of a Type II error (false negative). Conversely, if participants become accustomed to the experience, they are likely to be less fearful and thus the chance of a Type I error (false positive) is increased. This effect may be evident and explain the results found in the study by Walsh et al (1995a). There was a trend of decreasing mean VAS in all groups, including control, possibly indicating a familiarisation effect. Also, mean VAS was reduced to a greater extent in the placebo group compared to HF-TENS (Walsh et al 1995a). Adding in a familiarisation session and randomising the entry into each condition (as in the study by Chen and Johnson (2011)) can help reduce the impact of this phenomenon (Shanahan et al 2006). Overall, this well-designed and conducted study indicated a positive effect of LF-TENS on induced ischaemic pain.

Foster et al (1996) also examined the effects of different TENS stimulation settings on induced ischaemic pain. With the study design and parameters selected, the authors found no differences in measure of pain intensity or quality. The primary focus of this high quality study was to examine the effects of changing pulse duration. Four different combinations of TENS settings were chosen and assessed in a similar design to that employed by Walsh et al (1995a) (see Table 5.6). The settings tested align with the current guidance on the most efficacious TENS parameters although the combination of LF-TENS with short pulse duration (50µsec) is not advocated (Charlton 2005). The intensity of LF-TENS used is also not optimal. Similar to the study by Walsh et al (1995a), participants were encouraged to control their own intensity. However, for both types of TENS this was stated as 'strong but comfortable', not 'maximum tolerated' for LF-TENS. Also, as in the study by Walsh et al (1995a) the electrode placement was not ideal for both types of TENS. The researchers used points,

proximal to the cuff for stimulation (Table 5.6). This decision is suitable for LF-TENS but not for HF-TENS which should be applied over the painful area, in the case of the SETT, the forearm. The authors in the discussion address these limitations in settings of intensity and electrode placement and recommendations are made that future studies should examine stronger intensities and stimulation over the site of pain. This study also has the same limitations in terms of design as discussed with Walsh et al (1995a). Intervention was conducted secondary to baseline. In contrast to Walsh et al (1995a), no familiarisation effect is evident in the results presented. In general, the study by Foster et al (1996) is high quality study but limited in terms of TENS stimulation parameters employed which might explain the lack of hypoalgesic effects observed.

The study by Johnson and Tabasam (2003) was classified as low quality due to the lack of description of randomisation or double-blinding procedures (Table 5.5). The aim of the study was to compare the effects of HF-TENS and interferential current (another electro-physical modality) on ischaemic pain. HF-TENS was concluded to have no effect on ischaemic pain above placebo. However, the authors felt that the TENS parameters used were insufficient. The settings used are detailed in Table 5.6 and adhere to the guidance previously discussed so this conclusion is confusing. Nevertheless, the design of the experiment may have led to a Type II error as previously described. As the order of interventions was not randomised and the intervention conducted during the second SETT (24-48 hours after the first), participants, knowing what they were to experience, attributed more fear to the stimulus and thus reported higher scores of pain intensity, nullifying the hypoalgesic effects of TENS.

The study that scored the highest on the modified Jadad scale in terms of quality was that of Chen and Johnson (2011). The aim of this study was to build upon the research previously conducted and evaluate the effects of HF and LF-TENS on experimental ischaemic pain but with a special focus on the quality of the trial and thus the reliability and validity of the results. The conclusions drawn were that both types of TENS reduced pain intensity compared to placebo but HF-TENS was more effective than LF-TENS (Chen and Johnson 2011). One of the key improvements compared to the other studies was the sample size and

experimental design. Forty-eight participants (24 male) were recruited and entered into a double blind, repeated measures, experiment where order of entry into the three conditions (HF-TENS, LF-TENS and Placebo) was randomised along with participant group. This helped to reduce the chance of Type I or Type II errors, increase internal validity and reduce the chance of measurement bias. The TENS settings employed align with the guidance and current evidence, apart from intensity of LF-TENS which could be higher (Table 5.6). The statistics used to test for any effects were also very detailed and robust. Complex general linear models and post-hoc tests were used to test for within and between-group differences in VAS and SF-MPQ scores.

The possible limitations of this study are the version of the SETT used and the brevity of ischaemic pain induced. Similar to the study of Johnson and Tabasam (2003) from the same research centre, the authors employed the SETT procedure to the forearm and TENS electrodes to either side of the cuff (Table 5.6). The forearm SETT has both benefits and limitations. Originally devised due to participant reports of widespread paraesthesia with the upper arm SETT, the forearm SETT has been reported to induce pain in the region of the hand, similar in intensity to that when the cuff is applied to the upper arm (Johnson and Tabasam 2003). What is not clear however, is what pain is being induced and evaluated. Pertovaara (1984) described two distinct components of SETT-induced pain: mechanical cuff pain and ischaemic pain distal to the cuff. In the original model of the SETT (Smith et al 1966), the muscles being exercised were distal to the cuff and thus allowed to work freely in an ischaemic environment, inducing pain. In the forearm version of the SETT, the muscles being exercised by the handgrip exercises are, to a greater extent, underneath the cuff. Due to the pressure exerted by the cuff, these muscles may not be able to function as before and thus reduce the intensity, and possibly the quality of pain induced. Conversely, the severity of mechanical pain experienced may be increased. As the pressure is directly on the muscles attempting to work, the mechanical forces may be felt more acutely. Participants may therefore report a mixture of mechanical and ischaemic pain due to the proximity of the conflicting stimulations.

In the study by Chen and Johnson (2011), when pain was induced, participants were asked to continue for 2 minutes. As discussed above, this is understandable in terms of the overall study design although it could affect the conclusions relating to TENS. The maximum pain intensity reported was a mean VAS score with LF-TENS at 1 minute of 48.42 and a mean PRI score of 17.21 at baseline (Chen and Johnson 2011). This is similar to that reported by Walsh et al (1995a) for the mean VAS throughout 12 minutes of the SETT. This indicates that participants were experiencing similar levels of pain despite the minimal length of time. Unfortunately, the raw data from the study by Walsh et al (1995a) is not available to examine the development of pain over time. However, it has been noted in previous studies that ischaemic pain induced by the SETT gradually increases over time (Roche et al 1984; Johnson and Tabasam 2003). As the mean value of pain intensity over 12 minutes reported by Walsh et al (1995a) has been matched in the first minute by participants in the study by Chen and Johnson (2011) it suggests that the pain induced by the forearm SETT is in fact more severe than that produced by the upper arm SETT employed by Walsh et al (1995a). Overall, and despite these differences in pain induction, both types of TENS have been shown to be effective at reducing pain intensity in the most high quality study available.

#### 5.4.1.6: Summary:

---

The aim of this review was to evaluate the current evidence for the hypoalgesic effects of TENS on experimentally induced ischaemic pain in healthy volunteers. Six studies met the inclusion criteria and were assessed in terms of methodological quality and reported results.

All studies investigated a form of HF-TENS. Four out of the six studies found no effect of HF-TENS on either VAS or MPQ scores (Rosenblatt and Hetherington 1981; Walsh et al 1995a; Foster et al 1996; Johnson and Tabasam 2003). HF-TENS frequencies tested varied from 80-110Hz with the lower frequency proving the most effective application (Table 5.6 and 5.7). Chen and Johnson (2011) found that HF-TENS at 80pps reduced SPRI scores of the MPQ compared to placebo and VAS ratings compared to placebo and LF-TENS at 3pps.

Four of the studies also investigated the effects of LF-TENS on induced ischaemic pain (Roche et al 1984; Walsh et al 1995a; Foster et al 1996; Chen and Johnson 2011). Of these,

three reported hypoalgesic effects over control or placebo (Roche et al 1984; Walsh et al 1995a; Chen and Johnson 2011). LF-TENS settings varied within and between the studies with frequencies of 3-5Hz (Table 5.6).

Of the six studies identified for inclusion in this review, three were of low quality and results were often conflicting and confusing. Assessment of low quality most commonly reflected lack of double blinding procedures and limited statistical power due to small sample sizes and between-subject designs. The conflicting or negative results were most commonly as a result of poorly chosen TENS stimulation settings. Future research must aim to avoid these pitfalls by designing double-blinded, randomised, repeated measures experiments with sufficient sample size to detect effects. Also, by using standardised TENS settings and altering just one parameter each time, the specific effects and optimal settings for each parameter might be identified.

Overall, in the three high quality studies (Walsh et al 1995a; Foster et al 1996; Chen and Johnson 2011), two reported significant hypoalgesic effects of TENS for induced ischaemic pain. It can be concluded that, when using sufficient stimulation parameters in robust study designs, TENS is effective at reducing induced ischaemic pain in healthy volunteers.

The aim of this review was to establish the current state of the published evidence regarding TENS and laboratory-induced ischaemic pain. If achieved this would allow the evaluation of the current understanding of the effects of TENS on ischaemic pain and also provide some indication regarding which parameters have been found to be the most effective for the reduction of ischaemic pain. In the context of this thesis, this informs the development and design of studies investigating the effects of TENS for ischaemic pain.

Table 5.6: Overview of TENS parameters employed in the review

Study	TENS Parameters					Duration	SETT	n per group
	General	Frequency	Pulse	Intensity	Electrodes			
Rosenblatt and Hetherington 1981	HF-TENS Single vs. Dual channel	100Hz	40 µsec	Maximum tolerated	Single = 2 Dual = 4: Size not specified Axillary artery Circumferentially opposite	25mins: started just before SETT	250mmHg 20x30lb 25mins	10
Roche et al 1984	HF/HI-TENS	100Hz	1msec	HI=Max tolerated	2x2cm <sup>2</sup>	35 mins	250mmHg	12
	LF/HI-TENS	5Hz	100msec	LI=Just perceptible	Radioulnar Joint	(10mins prior to SETT)	20xMax	
	LF/LI-TENS	5Hz	100msec		Cubital fossa		25mins	
Walsh et al 1995a	HF-TENS	110Hz	287µsec	'Strong but comfortable' (participant controlled)	2x 2x2in	22mins	200mmHg	8
	LF-TENS	4Hz	287µsec		Erb's point Just lateral to C6 and 7	(10 mins prior to SETT)	20x75% max 12mins	

Table 5.6 (continued): Overview of TENS parameters employed in the review.

Study	TENS Parameters					Duration	SETT	n per group
	General	Frequency	Pulse	Intensity	Electrodes			
Foster et al 1996	HF-TENS	110Hz	200µsec	'Strong but comfortable' (participant controlled)	2x 3.5x5cm	30mins	200mmHg	8
	LF-TENS	4Hz	50µsec		Erb's point	(23mins	20x75%	
	Different pulse duration		200µsec		Just lateral to C6 and 7	prior to	max	
			50µsec			SETT)	12mins	
Johnson and Tasbasam 2003	HF-TENS	100Hz	200µsec	'Strong but comfortable' (participant controlled)	4x 4.5cm <sup>2</sup>	22mins	200mmHg	10
					Two above and 2 below cuff on ant and post forearm	(12 mins prior to SETT)	20x75% max 10mins	
Chen and Johnson 2011	HF-TENS	80Hz	200µsec	'Strong but comfortable'	4x 5cm <sup>2</sup>	20mins	200mmHg	48 (repeated measures)
	LF-TENS	3Hz	200µsec		Two above and 2 below cuff on ant and post forearm	(15mins before SETT)	15x75% max 2mins	

Table 5.7: Overview of the findings of the studies included in the review

Study	Findings
Rosenblatt and Hetherington 1981	No change in time to pain tolerance No difference in VAS scores (Student's t-test)
Roche et al 1984	LF/LI-TENS increased time to threshold and tolerance HF/HI-TENS increased time to tolerance, endurance and decreased MPQ-PRI scores (Student's t-test)
Walsh et al 1995a	LF/HI-TENS reduced mean VAS compared to control and HF-TENS Mean VAS decreased with P-TENS compared to HF-TENS LF/HI-TENS decreased VAS in minutes 7-9 compared to all No change in MPQ (1-way ANOVA)
Foster et al 1996	No differences in VAS or MPQ scores between groups or over time. (Difference scores and ANOVA)
Johnson and Tasbasam 2003	No difference in VAS scores from control or placebo No difference in SF-MPQ between groups (Difference scores and 2-way repeated measures ANOVA/ 1-way ANOVA for MPQ)
Chen and Johnson 2011	HF-TENS reduced VAS compared to LF-TENS and placebo VAS increased with placebo and even more with LF-TENS compared to control Both TENS reduced SPRI compared to placebo SPRI scores increased with LF-TENS compared to control



### 5.5: LOWER LIMB LABORATORY-INDUCED ISCHAEMIC PAIN:

---

IC pain most commonly occurs in the lower limb, and when standing. Despite these promising results of TENS in the upper limb as noted above, it is not known whether TENS will produce the same results in the lower limb. There are a number of important physiological differences between the upper and lower limb such as the composition of muscle fibre types and different vascular and neural networks (Johnson et al 1973; Scott et al 2001).

Johnson et al (1973) performed autopsy examinations of 36 muscles from 6 male subjects and found a larger proportion of type I muscle fibres in the lower limb compared to a larger proportion of type II (a and b) muscle fibres in the upper limb. Type II, or fast-twitch muscle fibres have been shown to have more capacity than slow-twitch fibres to work anaerobically due to a greater glycolytic potential (Zierath and Hawley 2004). In an ischaemic environment, as in laboratory-induced ischaemic pain, type I fibres may thus fatigue more rapidly and result in a greater accumulation of the by-products of anaerobic metabolism and a different experience of pain.

Due to this difference in muscle fibre composition and thus possibly development and experience of ischaemic pain, it is not clear whether TENS would produce the same effects as in the upper limb. In addition, IC pain occurs when walking. The need to function in pain adds an extra dimension to the experience, which is not replicated in the SETT. After the initial exercise, the upper limb is rested throughout the rest of the procedure. Requiring the limb to function during pain may affect the hypoalgesic effects of TENS.

---

#### 5.5.1: Pilot Studies of Lower Limb Laboratory-Induced Ischaemic Pain:

---

A series of pilot studies conducted at Queen Margaret University in healthy volunteers have adapted the upper limb SETT (Woolf 1979; Roche et al 2002) to the lower limb and applied it in supine or standing laboratory subjects (Roche et al 2007; Mackay et al, unpublished observations 2007; Simpson, unpublished observations 2007).

The first study developed the lower limb method in supine participants and compared outcomes between the standardised upper limb SETT procedure and the adapted lower limb SETT procedure. The outcomes were compared in terms of: a) tissue ischaemia as measured with Laser Doppler Flowmetry (LDF); b) pain intensity during ischaemia as measured with a Numerical Rating Scale (NRS) and c) subjective description of pain as measured with the MPQ (Roche et al 2007) (Table 5.8). The researchers found that the modified SETT successfully induced ischaemia in the lower limb, as measured by LDF. Despite this success, the induced ischaemia was recorded at a lower level than that measured in the upper limb. Also, the pain reported in the lower limb was found to be similar in quality but less intense than that in the upper limb (Roche et al 2007).

The second study examined the pain induced in the lower limb SETT in the sitting and standing subject to investigate the effects of body position on the pain reported (Mackay et al, unpublished observations 2007). The authors reported that pain intensity and time to pain threshold and tolerance increased when standing.

Most recently in the third study, the lower limb SETT methodology was developed in the standing subject, inducing pain similar in quality and intensity to the upper limb method (Simpson, unpublished observations 2007). Reliable levels of pain were induced in a repeated measures design and TENS was found to prolong time to pain tolerance.

The details of this series of pilot studies are summarised in Table 5.8.

Table 5.8: Summary of pilot studies investigating lower limb ischaemic pain

Study	Roche et al (2007)	Sweers, unpublished observations (2007)	Mackay et al, unpublished observations (2007)	Simpson, unpublished observations (2007)
<b>Study Design</b>	UL-SETT vs. LL-SETT	TENS for LL-SETT	Pain in LL-SETT	TENS for LL-SETT
<b>Participants</b>	10 males	21 females	20 males	17 females
<b>Position</b>	Supine	Supine	Sitting and Standing	Standing
<b>TENS</b>	None	HF-TENS over calf	None	HF-TENS over calf
<b>Outcome</b>	Pain Threshold	Pain Threshold	Pain Threshold	Pain Threshold
<b>Measures</b>	Pain Tolerance	Pain Tolerance	Pain Tolerance	Pain Tolerance
	Pain Endurance	Pain Endurance	Pain Endurance	Pain Endurance
	21-NRS	VAS at 1 minute intervals	VAS at 1 minute intervals	VAS at 1 minute intervals
	Post Occlusive Reactive Hyperaemic response (PORH) measured by Laser Doppler Flowmetry			
<b>Findings</b>	LL-SETT induces pain comparable to that with the UL-SETT	HF-TENS increased time to pain threshold and tolerance compared to no-TENS control	LL-SETT induced pain in the sitting and standing subject however, intensity was greater when standing.	TENS increased pain tolerance but not threshold, endurance or intensity

---

### 5.5.2: TENS for Laboratory-Induced Lower Limb Ischaemic Pain:

---

Two of these pilot studies also conducted preliminary investigations into the effect of TENS on the induced ischaemia (Roche et al 2007; Simpson, unpublished observations 2007). When compared to control, TENS was found to increase the time before the report of 'pain threshold' and 'pain tolerance' but it did not reach significance in supine and standing subjects (Roche et al 2007; Simpson, unpublished observations 2007). Despite these preliminary indications of TENS efficacy for lower limb induced ischaemic pain, the generalisation of these results to a wider population and to clinical IC pain is limited due to their low sample sizes and the need for further control of the experimental design. Further laboratory research must address methodological weaknesses i.e. introduce larger sample size and a standardised, randomised and controlled design including placebo TENS before trialling TENS in a clinical IC pain population.

---

### 5.5.3: Future Directions:

---

The studies discussed here have completed important groundwork, refining the lower limb method, identifying limitations and recommending areas for development. A further study that begins to address these limitations and refines the procedure would be beneficial as a preliminary validation of this lower limb model. A valid and reliable method of inducing lower limb ischaemic pain could be useful for investigation of the qualities of ischaemic pain, and how those qualities respond to TENS without the influence affective-evaluative impact of chronic pain. It is anticipated for example that laboratory-induced ischaemic pain may have similar sensory-discriminative qualities to IC but have fewer affective-motivational and cognitive-evaluative components. Such a non-chronic profile of the sensory-discriminative components of ischaemic pain could be a useful way to examine how TENS affects the common sensory experience of IC pain.

---

## 5.6: CONCLUSION:

---

Currently there is an established method for inducing ischaemic pain in the upper limb. TENS has been shown to be effective in reducing this pain. This cannot be extrapolated to the clinical population however, due to the physiological differences between the upper and

lower limbs. There has been initial development of a lower limb method of inducing ischaemic pain. TENS has been shown to be effective in reducing this pain. These results cannot be extrapolated to the clinical population either however, due to methodological limitations. The lower limb method requires development and the effect of TENS on the pain induced needs to be investigated.

#### 5.7: CHAPTER 5 SUMMARY:

---

The aim of this chapter was to explore the concept of laboratory-induced pain as a possible method that could help address the two central aims of this thesis. Laboratory-induced pain has been shown to be useful in the study of pain syndromes and for the testing of interventions. Experimental pain is useful as it allows study of the pain experience without the confounding comorbidities of clinical pain and affords some control over the quality of pain experienced. Of the different methods of inducing experimental pain, the ischaemic pain model (SETT method) appears to induce pain through similar physiological mechanisms to that experienced with IC. The SETT method induces pain in the upper limb of healthy volunteers in sitting and has been used to examine the pain experience and test interventions including TENS. A systematic review of the effects of TENS showed that when appropriate stimulation parameters were employed, TENS has a hypoalgesic effect on the SETT-induced ischaemic pain.

IC pain however, occurs in the lower limb and when standing, both of which factors may alter the pain experience. With this in mind, a series of pilot studies have adapted the SETT method to a standing, lower limb application. The effect of TENS on this lower limb ischaemic pain was investigated with trends towards hypoalgesia reported. Prior to further study or adoption of this lower limb method, it is important that the procedure is refined and the reliability of the induced pain investigated. Also further study is required that examines the hypoalgesic effects of TENS in larger populations and to be accepted as a pre-clinical model of IC pain, the subjective qualities of the pain experience induced by this lower limb method must be compared to those in IC pain.

## CHAPTER 6: LITERATURE REVIEW SUMMARY AND STUDY RATIONALE

---

### 6.1: AIM OF CHAPTER 6:

---

The aim of this chapter is to summarise the aims and objectives discussed in Chapter 1 whilst integrating the literature and concepts discussed in Chapters 2-5. A series of studies designed to address these aims will then be discussed, indicating how each study is designed to address the questions of this programme of research.

### 6.2: SUMMARY OF LITERATURE REVIEW AND RESEARCH QUESTIONS:

---

The clinical problem of IC is well established and associated with decreased physical and psychological function and decrease in quality of life. Understanding of the IC pain experience is limited and issues have been identified with current management strategies. Pain, and especially chronic pain, is a complex, multidimensional experience with sensory-discriminative, affective-motivational and cognitive-evaluative components. These components are affected by numerous psychological and social factors including situation, beliefs, experience, culture, attention and behaviour. Understanding the subjective descriptive qualities and the associated psychosocial factors of any pain experience is valuable when attempting to understand observed effects and designing management strategies. Currently IC pain is lacking in this respect. A recording and evaluation of the subjective descriptions of IC pain could be an effective means of improving the understanding and management of patients with IC.

Current management of IC consists of risk factor modification, exercise therapy and pharmacological management. All of these management strategies have been shown to be effective although one problem that has been identified is a lack of adherence to exercise therapy. The experience of IC pain has been identified as one possible explanation for this poor adherence to exercise therapy but no hypoalgesic interventions have been investigated in an attempt to reduce the burden of IC pain. TENS is a low-cost, non-pharmacological hypoalgesic intervention shown to have hypoalgesic effects for other chronic pain conditions. TENS has been shown to have hypoalgesic effects on induced

ischaemic pain in the upper limb of healthy volunteers. TENS could be useful as an adjunctive intervention for IC that reduces the experience of pain and increases walking performance. It has not however been investigated for induced ischaemic pain in the lower limb or for IC pain.

There are therefore two central research questions addressed in this thesis:

- What qualities characterise the subjective description of IC pain?
- What are the effects of TENS on measures of pain and walking performance in patients with IC?

### 6.3: AIMS AND OBJECTIVES OF THIS PROJECT:

---

From these two questions, the aims of this project are formulated. One aim is to investigate the subjective description of the multidimensional qualities of ischaemic pain. The second aim is to investigate the hypoalgesic effects of TENS on lower limb ischaemic pain and walking performance in patients with IC.

These aims can be addressed through four clear objectives that are linked to four distinct studies:

#### **Objective 1: to develop and validate the mSETT in the lower limb of healthy volunteers.**

This objective aims to establish the mSETT as a reliable method of inducing ischaemic pain in the lower limb of healthy volunteers. This will contribute to both aims of the project by establishing a method that allows investigation of the subjective descriptive qualities of lower limb ischaemic pain and examination of the effects of TENS on these qualities.

- Study 1: An examination of the test re-test reliability of the ability of the mSETT to induce consistent levels of pain was conducted (Chapter 7). A laboratory study is proposed that examines the pain induced by the mSETT in healthy volunteers. The ability of the mSETT to induce comparable levels of pain on separate occasions will be examined in a preliminary validation study.

**Objective 2: to investigate the effects of TENS on the pain induced by the mSETT.** This objective contributes evidence regarding the effects of TENS on lower limb ischaemic pain and more specifically which aspects of the pain experience are affected by TENS intervention. Again this objective will contribute to both aims as MPQ descriptions of ischaemic pain will be recorded and the effects of TENS on lower limb ischaemic pain investigated.

- Study 2: An investigation into the hypoalgesic effects of HF-TENS on mSETT induced pain in healthy volunteers (Chapter 8). Following the validation study another laboratory study is proposed that investigates the effects of HF-TENS and Placebo TENS (P-TENS) on reports of mSETT-induced pain intensity and quality as measured by the MPQ.

**Objective 3: to investigate the effects of TENS on pain and walking performance in patients with IC.** This objective is central to the attempt of this thesis to address the identified clinical problem of IC. Both aims will be addressed by investigating the effects of TENS on IC pain and walking performance and recording of the descriptions of clinical ischaemic pain with the MPQ.

- Study 3: An investigation into the hypoalgesic effects of HF and LF-TENS on measures of pain and walking performance in patients with IC (Chapter 9). A clinical, Medical Research Council (MRC) phase IIa, 'proof of concept' study is proposed that investigates the effects of TENS on walking performance in patients with PAD and IC. This study will also examine the psychosocial aspects of IC pain and relationships to walking performance.

**Objective 4: to record and compare the subjective descriptions of the pain experience associated with IC and mSETT induced pain.** This objective will specifically address the first aim of the project: to investigate the subjective description of ischaemic pain. By comparing descriptions of pain between the clinical IC population and healthy volunteers experiencing the mSETT, the subjective descriptions of lower limb ischaemic pain can be explored.



- Study 4: A post hoc examination of the pain descriptions as recorded by the MPQ in patients with IC and healthy volunteers experiencing mSETT induced pain (Chapter 10). The specific subjective nature and quality of IC pain will be compared to that induced by the mSETT.

#### 6.4: CHAPTER 6 SUMMARY:

---

The aim of this chapter was to summarise the aims and objectives discussed in Chapter 1 whilst integrating the literature and concepts discussed in Chapters 2-5. After reviewing the literature, two clear research questions have been identified. In an attempt to address these questions, research aims and objectives are proposed. The following five chapters will describe and discuss the execution of this plan and explore the results of each stage. Finally, the last chapter will reflect back on these original aims and discuss any conclusions that can be drawn from the work undertaken.

## CHAPTER 7: EXPERIMENT ONE - TEST-RETEST RELIABILITY OF THE MODIFIED SETT (MSETT)

---

### 7.1: AIM OF CHAPTER 7:

---

TENS is a possible useful adjunctive intervention for clinical lower limb ischaemic pain in the form of IC. Prior to clinical investigation, it is common and prudent for novel hypoalgesic interventions to be tested on a pre-clinical model of pain. The SETT method is an established method for inducing ischaemic pain in healthy volunteers. TENS has been shown to reduce induced ischaemic pain in the upper limb of healthy volunteers using the SETT method. It has not been tested for lower limb ischaemic pain. Due to the physiological differences between the upper and lower limbs, an experimental method of inducing lower limb ischaemic pain would be useful to test the effects of TENS prior to clinical evaluation in IC pain.

A series of pilot studies have modified the SETT to a lower limb application. The test-retest reliability of pain induced by the lower limb SETT (mSETT) method has not been investigated. This issue requires consideration for the development of the mSETT as an experimental model of pain. Therefore, the following investigations were undertaken to address this reliability issue and thus address the research aim to develop a robust experimental method of inducing lower limb ischaemic pain.

The aim of this chapter is to describe the investigation of the test-retest reliability of the mSETT. The methods employed will be described and the findings discussed.

### 7.2: METHOD:

---

#### 7.2.1: Design:

---

This study was designed to assess the test-retest reliability of the mSETT method of inducing pain, thus informing the substantive study examining the effect of TENS on induced, lower limb ischaemic pain as described in Chapter 8 of this thesis. Each participant completed the protocol on two separate occasions, at least three weeks apart, with the same investigator.

Data were collected such that the test-retest reliability could be estimated through Intraclass Correlation Coefficient (ICC). The study was granted ethical approval by the University Research Ethics Committee.

---

#### 7.2.2: Participants:

---

A convenience sample of 11 participants (7 male) with a mean age of 28 years (range = 21-35 years) was recruited from the University's student population. Each participant received an information sheet and exclusion criteria questionnaire (Appendix 4 and 5). No participant was excluded from the study, the experimental procedure was explained and written informed consent was obtained (Appendix 6).

---

#### 7.2.3: Measures:

---

##### 7.2.3.1: Pain:

---

Pain threshold was defined as the time in seconds to "the moment discomfort turns to pain" and was indicated by the participant saying, "pain now" (Melzack and Wall 1996; Roche et al 2002). Pain tolerance was defined as the time in seconds to "the moment the subject reports that he is no longer able to tolerate the pain" and was indicated by the participant stating, "stop" (Melzack and Wall 1996; Roche et al 2002). Pain endurance was defined as the time in seconds between pain threshold and pain tolerance (Roche et al 2002).

Pain intensity was measured using a 21-point Numerical Rating Scale (21-NRS): a numerical scale ranging from 0 to 20, with labels of "no pain" and "unbearable pain" respectively. Participants were asked to choose a number between 0 and 20 which best reflects their current pain intensity. The NRS has been found to be valid, reliable and practical for use in both laboratory and clinical pain (see section 3.5.1) (Jensen et al 1986; Bolton and Wilkinson 1998).

A McGill Pain Questionnaire (MPQ) was administered retrospectively, within 5 minutes of the participant reporting 'pain tolerance'. The participant was asked to describe the pain they experienced at pain tolerance. The MPQ is valid and reliable in the laboratory setting

(Klepac et al 1981) and can provide information regarding the pain qualities and intensity associated with different pain syndromes (Dubuisson and Melzack 1976; Jerome et al 1988; Katz and Melzack 1991; Dworkin et al 2009). Pain Rating Index (PRI) scores from the MPQ were recorded and analysed as a measure of the sensory, reactive and overall nature of the ischaemic pain at the point of tolerance (Melzack 1975; Roche et al 1984).

#### 7.2.3.2: Psychosocial:

---

When measuring any pain experience it is essential that psychosocial factors are considered and recorded (Katz and Melzack 1999). Psychological factors related to pain have been shown to affect sensitivity to experimental pain (Rainville et al 2005; George et al 2006; Hirsh et al 2008).

Specifically, fear of pain and pain self-efficacy independently predict time to pain threshold and tolerance in healthy volunteers experiencing laboratory-induced pain (George et al 2006; Vancleef and Peters 2011). Therefore, in the current study, measures of pain self-efficacy and fear of pain were employed to quantify the levels of these psychological variables between participants.

Pain self-efficacy was measured using the Pain Self-Efficacy Questionnaire (PSEQ) (Nicholas, 2007). This measure was recorded at the end of the testing session with each participant rating how they felt the pain they had just experienced would affect them if suffered daily. Pain-related fear was measured using the Fear of Pain Questionnaire (FPQ) (McNeil and Rainwater, 1998).

#### 7.2.3.3: Physiological:

---

Physiological measures were used to monitor each participant's physiological reaction to ischaemia and pain. There are no established guidelines for monitoring the systemic response to ischaemia. Recent literature has highlighted some systemic effects of tourniquet use. Due to the increase in circulating blood volume, pressor response and the response to pain, heart rate and systolic blood pressure can be elevated through inducing

ischaemia via tourniquet (Kam 2007). Therefore, blood pressure, heart rate and oxygen saturations were measured throughout the experimental procedure and the experiment was stopped immediately if any were outwith normal limits. Blood pressure was measured every 2 minutes using a digital blood pressure monitor (UA-767PAC, A&D Medical, Tokyo, Japan). A systolic pressure of 30mmHg above or below resting pressure acted as a cut-off for the procedure and the cuff was deflated immediately. No testing sessions were terminated due to a change in blood pressure. Participants' heart rate (HR) and oxygen saturations (SpO<sub>2</sub>) were measured continuously throughout the experimental procedure using a vital signs monitor (Vital Signs Monitor 300 Series, Welch Allyn, Bucks, UK). A normal range of more than 70% age-related maximum HR (maximum HR = 220-age) and less than 95% SpO<sub>2</sub> was used and the experiment was stopped if the readings strayed outwith these values.

---

#### 7.2.4: Study Procedure:

---

Each participant attended for testing on two occasions, at least three weeks apart, for approximately 1 hour. Each testing session was divided into three sections (Figure 7.1).

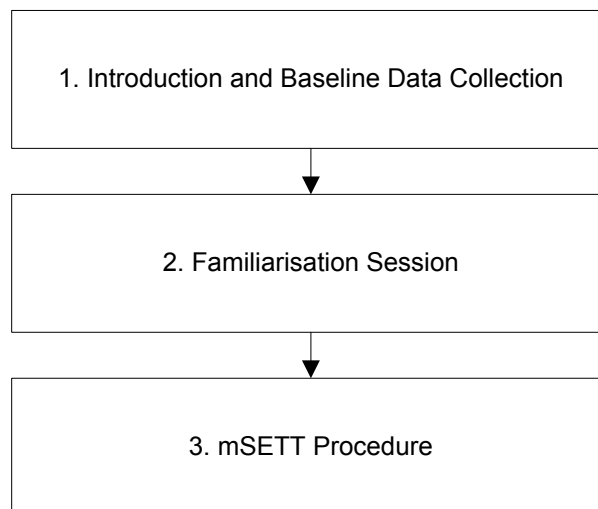


Figure 7.1: Experiment procedure.

##### 7.2.4.1: Introduction and Baseline Data Collection:

---

Participant descriptive data was recorded including date of birth, height, weight, heart rate, blood pressure, oxygen saturations and the circumference of their non-dominant thigh

(15cm above the proximal border of the patella with the knee resting in extension on the plinth).

#### 7.2.4.2: Familiarisation Session:

---

The participant completed a familiarisation session where the mSETT procedure was followed as detailed in section 7.2.4.3, with three exceptions:

1. Participants rested for 5, rather than 20 minutes prior to the mSETT as no reports of pain were being recorded i.e. the full rest period was not required.
2. The procedure was stopped 30 seconds after pain threshold rather than continuing to pain tolerance so that the participants did not become fatigued but managed to experience the nature of the development in pain intensity
3. No measures of pain were recorded as this session aimed just to allow the participant to experience the sensation.

Any participant questions or errors in experimental technique were addressed prior to commencing the procedure for the full testing session.

#### 7.2.4.3: mSETT Procedure:

---

A modified lower limb SETT (mSETT) was used to induce pain for a maximum duration of 20 minutes. This was adapted from the standardised upper limb SETT (Woolf 1979; Roche et al 1984; Roche et al 2002).

The upper limb SETT procedure, although employed with different parameters in different publications, has six common sequential components (Figure 7.2): 1) Rest period; 2) Desanguination; 3) Occlusion of blood flow; 4) Submaximal effort exercise; 5) Period of induced pain and 6) Release occlusion of blood flow.

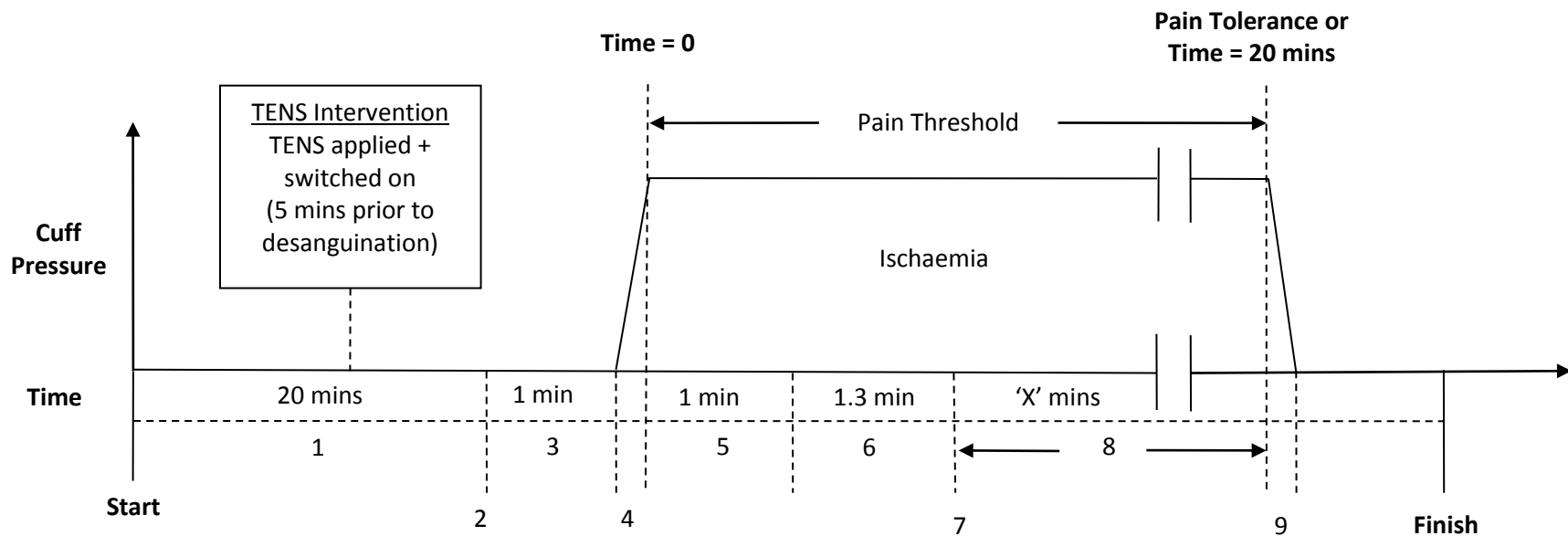


Figure 7.2: Modified Submaximal Effort Tourniquet Test (mSETT) procedure. Key: 1-Rest Period; 2-Limb Elevated; 3-Desanguination; 4-Cuff Inflated; 5-Standing in test position and backpack on; 6-Single-leg heel raise exercises; 7-Backpack removed; 8-21-NRS at irregular intervals; 9-Cuff Deflated over 2 mins.

The familiarisation session consisted of only 5 minutes rest period and terminated 30 seconds after pain threshold reported.

The baseline session followed the procedure but no TENS was applied.

The TENS session was the same as the baseline session except TENS was applied 5 minutes prior to cuff inflation and continued throughout.

### Rest Period:

---

After baseline measurements of heart rate (HR), blood pressure (BP) and saturation of oxygen ( $\text{SaO}_2$ ), the participant was asked to rest on the plinth, in a supine position, for 20 minutes. During this time, participants were asked to “close their eyes and rest” (Figure 7.3).

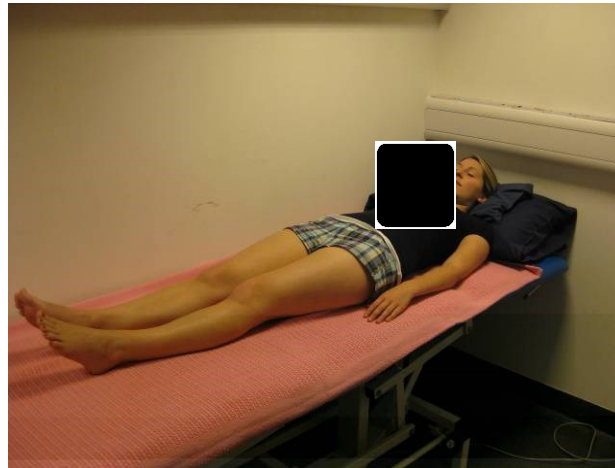


Figure 7.3: Participant relaxation, supine on plinth

After 15 minutes of relaxation on the plinth, the elastic bandage (Tubigrip: Size E, Seton Healthcare Group, Oldham, UK) and sphygmomanometer (20cm width; Bainbridge™, Trimline Medical Products, NJ, USA) were positioned on the participant's non-dominant lower limb (Figure 7.4).



Figure 7.4: Equipment placed on the participant's non-dominant lower limb with the sphygmomanometer cuff proximal to the popliteal crease



### Desanguination:

---

After 20 minutes of the rest period the plinth was raised so that the participant's legs were positioned at more than or equal to 45 degrees of hip flexion (Figure 7.5). This position was held for 60 seconds, after which the sphygmomanometer cuff was inflated.



Figure 7.5: Desanguination of the participant's limb with the equipment in place

### Occlusion of Blood Flow:

---

The cuff was inflated to 40mmHg above the participant's baseline systolic BP over 30 seconds with the limb in the above position. Once the cuff had reached the set pressure the stopwatch was started. The participant's legs were then lowered and they were helped into a standing position at the side of the plinth (Figure 7.6).

In the standing position the participant was asked to place their dominant foot on mechanical weighing scales. These scales were used to provide immediate feedback to the participant and researcher regarding the amount of weight being supported by the dominant leg. The participant was asked to keep the reading on the scale below 5kg. This technique was employed to help standardise the experimental procedure and encourage the participants to maintain their body weight through the leg being tested. Nevertheless,

the participant was instructed to use the support on either side of their body if required for safety.



Figure 7.6: Participant standing next to plinth with cuff in place, dominant leg on weighing scales and support on either side

#### Submaximal Effort Exercise:

Once the participant was positioned in standing, a weighted backpack was placed on their back (Figure 7.7). This was a standard backpack (Pax 25; Lowe Alpine International, Treviso, Italy) with 40kg of weight secured inside (total weight 40.5kg). The researcher lifted the backpack from the floor and helped the participant position it in place on their back and adjust the straps for comfort.

The time from completion of cuff inflation to commencing the exercises was always 1 minute.

The participant completed 20 repetitions of single-leg heel raises. A series of tones on a recording instructed the participant when to start and stop each exercise. When the tone sounded the participant plantar-flexed their non-dominant ankle and raised their heel off the ground (Figure 7.8). This position was held for the duration of the tone (2 seconds).

When the tone ceased, the participant relaxed their heel back down to the ground for the duration of the relax phase (2 seconds) (Figure 7.9).



Figure 7.7: The weighted backpack on the participant's back



Figure 7.8: Heel raise exercise. Contraction phase with the non-dominant (left) heel raised off the ground. The dominant heel is raised in order to maintain minimal contact with the scales and ensure the leg being tested is performing maximal weight bearing.



Figure 7.9: Heel raise exercise- relax phase with the non-dominant (left) heel returned to the ground

In summary, the submaximal effort exercise was single-leg heel raises mainly achieved using contraction of the muscles of the non-dominant lower limb. The participants performed 20 repetitions of 2sec/2sec, (contraction/relax) against their body weight and 40.5kg of the backpack.

#### Period of Induced Pain:

---

Once the participant had completed the exercises the backpack was removed by the researcher and they were instructed to stand as still as possible, only on their non-dominant leg for the rest of the procedure (Figure 7.6). The participant was also instructed to “keep the knee of their non-dominant leg ‘unlocked’ throughout” i.e. in a small amount of knee flexion (Figure 7.10). The rationale for this was to help ensure that the muscles of the leg being tested were actively contracting throughout the procedure and thus working in an ischaemic environment. The researcher monitored knee flexion throughout and prompted the participant if required.



Figure 7.10: Experimental position with the participant's non-dominant knee 'unlocked' i.e. in a small amount of knee flexion during the experimental procedure

The participants remained in this position throughout the experimental procedure. They were instructed to report pain threshold and pain tolerance. The participant indicated these points by saying "pain now" and "stop" respectively. Perceived pain intensity was recorded throughout with the 21-point Numerical Rating Scale (21-NRS): a numerical scale ranging from 0 to 20, with labels of "no pain" and "unbearable pain" respectively. The participant rated their pain at intervals using the 21-NRS, prompted by the audio track. These ratings were at fixed, irregular intervals of 30, 35, 40, or 45 seconds. These intervals were irregular in sequence but the same in each test to allow comparison. The irregular intervals were used with the aim of blinding the participant to how long they had tolerated the pain. The recording asked them to "rate their pain on a scale of 0-20 where 0 represents no pain at all and 20 represents the point of unbearable pain".

The NRS has been found to be the superior method of rating pain intensity in terms of validity, reliability and practicality compared to VAS, box scales and verbal rating scales

(Jensen et al 1986, Bolton and Wilkinson 1998). The use of 21 levels provides the optimum sensitivity to changes in pain intensity (Jensen et al 1994).

---

#### Release Occlusion of Blood Flow:

---

When the participant reached a score of 20 on the 21-NRS or reported Pain Tolerance by saying, “stop”, the experiment was ceased immediately. The cuff was deflated, the time recorded and the participant helped to sit back on the plinth. The equipment was removed and the participant instructed to rest on the plinth. After the participant had rested for 2 minutes, the researcher administered an MPQ asking the participant to describe the pain they experienced at the point of Pain Tolerance.

---

#### 7.2.5: Statistical Analysis:

---

Graphical analysis of raw test-retest pain data and intraclass correlation coefficient analysis was used to examine the test-retest reliability of the mSETT. A two-way, mixed effects Intraclass Correlation Coefficient (ICC) was selected (Random effect = participant, Fixed = rater). An ICC value of more than 0.6 (defined as ‘substantial’ reliability (Eliasziw et al 1994)) was set as the minimal acceptable level. Confidence Intervals (CI) at 95% were computed for the ICC values to identify the precision of the reliability coefficient and the limits within which the true typical error in the population was likely to reside. The standard error of measurement (SEM) was calculated for the change values to provide a quantitative indicator of the test-retest reliability of the mSETT and the measurement of pain threshold, tolerance and endurance. A repeated measures ANOVA was used to test for variation in the measures between trials. Data were analysed using Microsoft Excel® 2003 and SPSS Version 17.

### 7.3: RESULTS:

---

The participants were 11 healthy volunteers (7 male, 21-35 years) without previous experience of TENS or any known pathology or contraindication to the mSETT or TENS. No participant dropped out and none were excluded from analysis.

Individual participant data for both trials is displayed in Table 7.1 and Figures 7.11-13. Time taken to report pain threshold and tolerance were similar between trials for each participant. The positive mean change for each of the measures indicates a possible practice or familiarisation effect with the mSETT.

Scatter plots of individual scores for each measure are shown in Figures 7.14-7.16. Repeated measures ANOVA showed no differences between the values and ICC estimates for each of the outcomes are detailed in Table 7.2 ( $F_{10,10} = 6.561, p = .003$ ;  $F_{10,10} = 25.764, p < .001$ ;  $F_{10,10} = 24.715, p < .001$ ). Estimates of test-retest reliability were satisfactory with coefficients more than 0.7 for all three measures.

The ICC estimate for pain threshold was the lowest of the outcomes with a wide 95% CI (Table 7.2). This indicates 'substantial' reliability although the 'true' population estimate may be considerably different (95%CI ICC = 0.28-0.92).

The 95% CI's were narrow for pain tolerance and endurance, indicating good precision of the correlation estimates. The Standard Error of Measurement (SEM) (measured in seconds) indicates the degree of change, which represents 'real' variation rather than measurement error (Atkinson and Nevill 1998).

Table 7.1: Individual participant data for change in each measure with the mSETT.

Participant	Change (Trial 2-Trial 1)		
	Threshold (secs)	Tolerance (secs)	Endurance (secs)
<b>1</b>	9	9	0
<b>2</b>	11	153	142
<b>3</b>	44	105	61
<b>4</b>	3	12	9
<b>5</b>	14	6	-8
<b>6</b>	-19	50	69
<b>7</b>	20	165	145
<b>8</b>	9	48	39
<b>9</b>	29	52	23
<b>10</b>	-5	27	32
<b>11</b>	-13	15	28
<b>Mean</b>	9.3	58.4	49.1
<b>SE</b>	5.46	17.30	15.72

Table 7.2: ICC estimates for time to pain threshold, tolerance and endurance (measured in seconds).

	Threshold	Tolerance	Endurance
<b>Mean Trial 1 (SD)</b>	118.1 (27.8)	427.5 (139.4)	309.4 (119.5)
<b>Mean Trial 2 (SD)</b>	127.4 (21.6)	485.8 (156.8)	358.5 (143.7)
<b>Mean Difference (SD)</b>	9.3 (18.1)	58.4 (57.4)	49.1 (52.1)
<b>ICC</b>	0.74	0.93	0.92
<b>95% CI</b>	0.28-0.92	0.75-0.98	0.74-0.98
<b>SEM (secs)</b>	14.18	41.49	40.65
<b>95% SEM (secs)</b>	28.36	82.58	81.30
<b>SEM as % of mean</b>	12.0	9.71	13.1



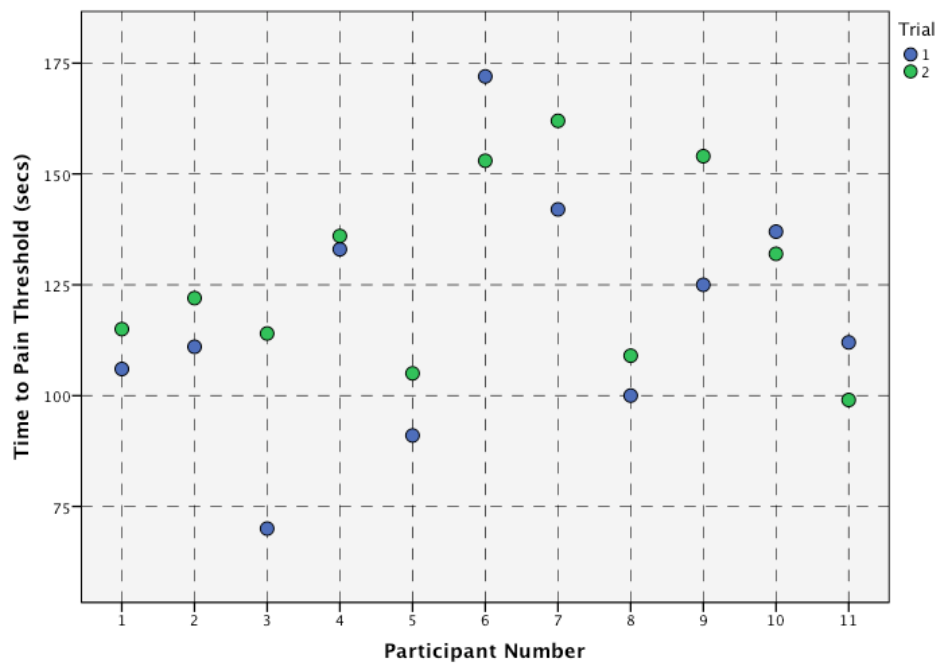


Figure 7.11: Individual participant data for time taken to report Pain Threshold (secs) in both trials.

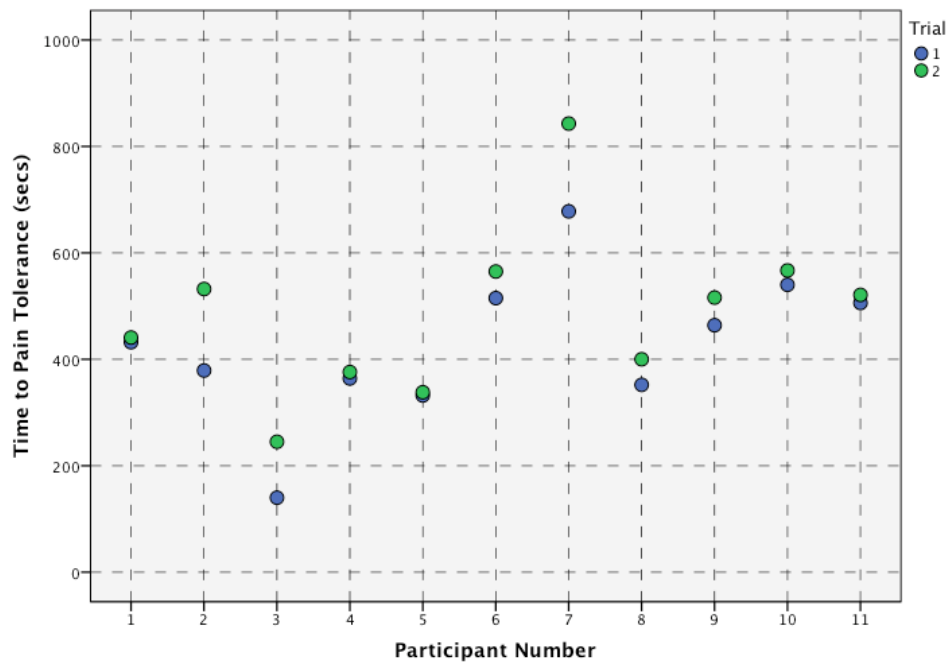


Figure 7.12: Individual participant data for time taken to report Pain Tolerance (secs) in both trials.

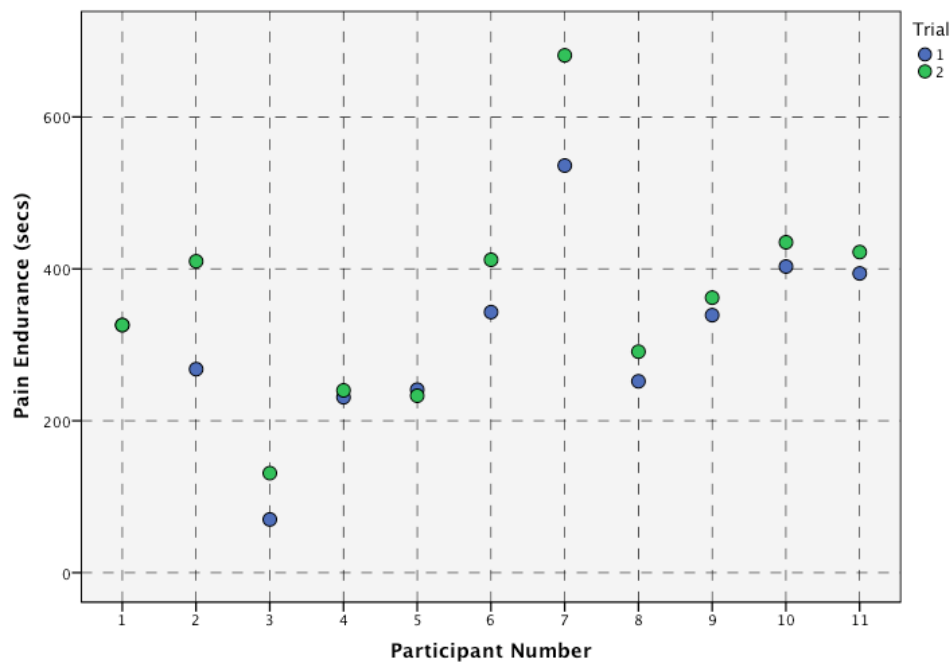


Figure 7.13: Individual participant data for Pain Endurance (secs) in both trials.

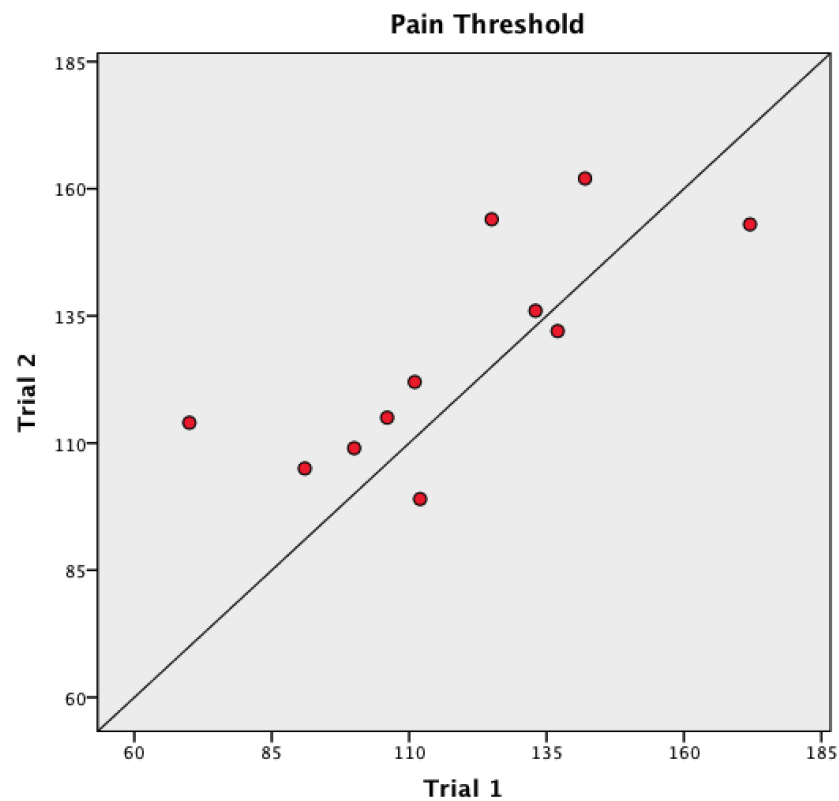


Figure 7.14: Scatterplot of time taken to report pain threshold in both trials. Line represents  $y=x$ .

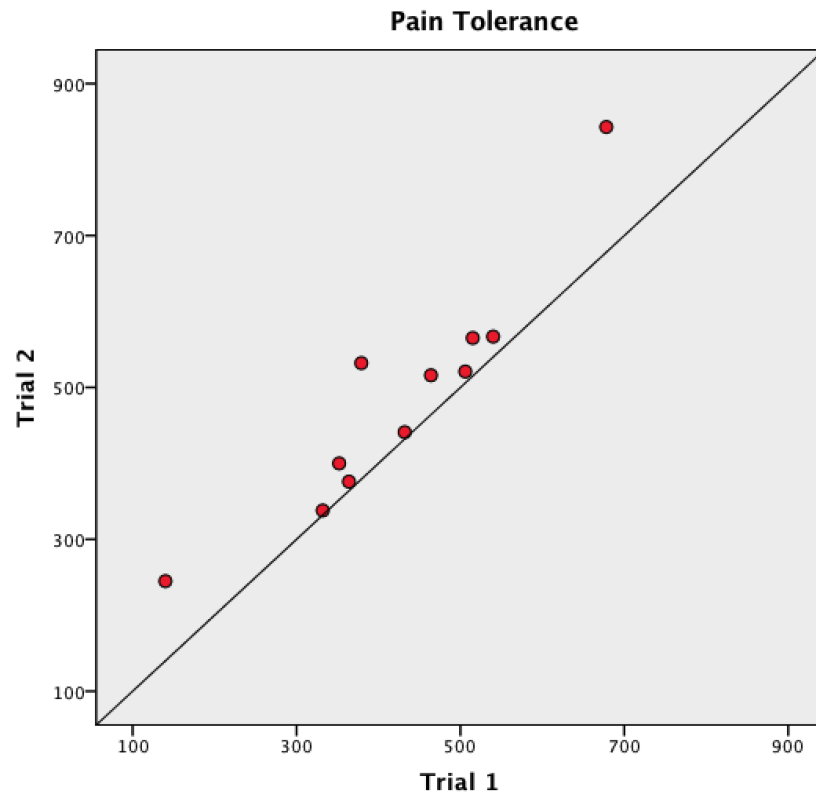


Figure 7.15: Scatterplot of time taken to report pain tolerance in both trials. Line represents  $y=x$ .

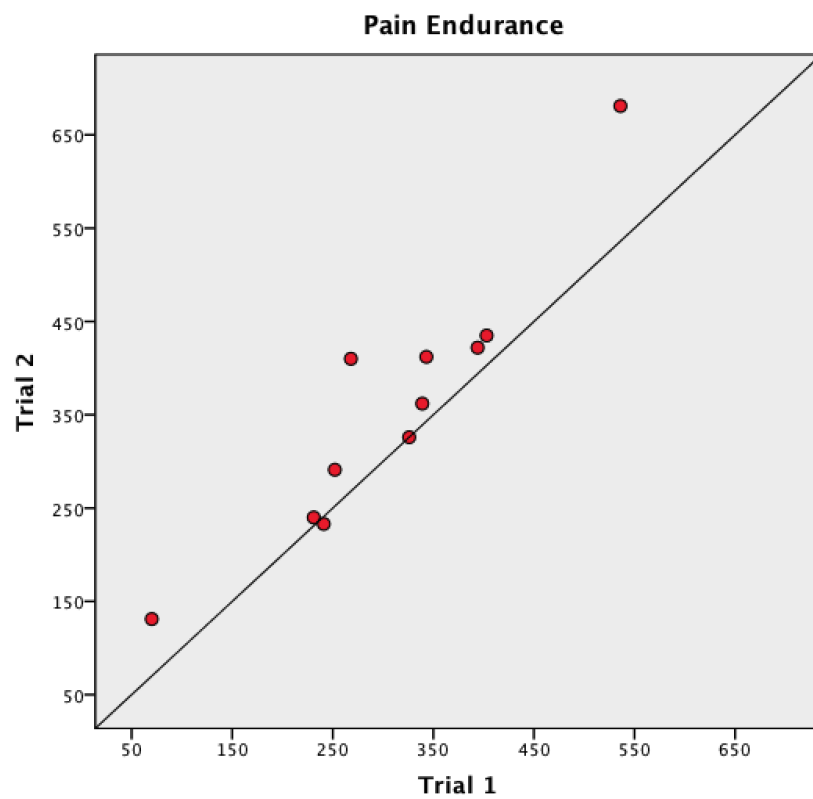


Figure 7.16: Scatterplot of pain endurance in both trials. Line represents  $y=x$ .

#### 7.4: DISCUSSION:

---

The value of an experimental pain method is its ability to reduce the erroneous variables inherent in clinical pain, and provide a platform for the investigation of the pain induced (Woolf 1979). An experimental method of inducing pain must therefore have good test-retest reliability in terms of the pain induced.

The results of this study indicate that participants experiencing mSETT-induced pain report comparable levels of pain on separate occasions. The intra-rater ICCs were excellent for time to report pain tolerance and pain endurance with the relatively narrow CIs showing the high degree of accuracy of the correlation estimates (Table 7.2). The ICC for pain threshold was also substantial however; the 95%CI was somewhat larger than with pain tolerance or endurance (Table 7.2). This suggests that even though the measurement of pain threshold with the mSETT is reliable, measures of pain tolerance and endurance are more so and thus should be used as primary outcomes for any studies employing the mSETT. This is a similar finding to that of Nicolai et al (2009b) with the graded treadmill test. In this test of clinical ischaemic pain, there is greater variability in the measure of pain threshold (Initial Claudication Distance (ICD)) compared to pain tolerance (Absolute Claudication Distance (ACD)).

The SEM for each measure shows small variability with each less than 14% of the mean. This highlights a consistency of pain reported by the participants during the mSETT procedure. The mSETT is therefore an appropriate method of inducing experimental pain in this population.

There is no published literature that examines the test-retest reliability of the pain induced by the mSETT in the lower limb of healthy volunteers. The current study has found that by following a specific experimental protocol, a consistent intensity of pain can be induced in the same individual on two separate occasions.

### 7.5: IMPLICATIONS AND CONCLUSIONS:

---

The reliability of a measure is linked to the specific population and the specific conditions in which one wishes to apply the measure (Streiner and Norman 2008). This study contributes evidence that participants undergoing the mSETT procedure report consistent and reliable levels of pain tolerance and endurance.

### 7.6: CHAPTER 7 SUMMARY:

---

The aim of this chapter was to describe the investigation of the test-retest reliability of the mSETT. This investigation has shown that mSETT induces comparable levels of pain intensity over two occasions. Time taken to report pain threshold, pain tolerance and pain endurance was similar within participants on two separate sessions.

The mSETT is therefore a reliable method of inducing pain in the lower limb of healthy volunteers and as such can be used to investigate the effects of interventions. The next chapter describes such an investigation. The effects of TENS on lower limb ischaemic pain will be examined using the mSETT as the method of inducing ischaemic pain in the lower limb of healthy volunteers.

## CHAPTER 8: EXPERIMENT TWO - THE EFFECTS OF TENS ON MSETT-INDUCED PAIN

---

### 8.1: AIM OF CHAPTER 8:

---

Prior to the investigation of the effects of TENS on clinical IC pain, robust investigation into the effects of TENS on lower limb ischaemic pain in a more controlled laboratory environment is indicated. The effects of TENS on experimentally induced, lower limb ischaemic pain have been previously investigated in small, pilot studies with varying methodologies (Roche et al 2007; Simpson, unpublished observations 2007). Promising hypoalgesic results have been observed, although methodological weaknesses limit the strength of the conclusions. In the previous chapter, the mSETT procedure was found to be a reliable method of inducing lower limb ischaemic pain in healthy volunteers. The study described in this chapter, aims to address the limitations of the previous investigations and examine the effects of TENS on mSETT-induced, lower limb pain in standing, healthy volunteers.

The aim of this chapter is to investigate mSETT-induced, lower limb ischaemic pain and the effects of High Frequency (120Hz) TENS (HF-TENS) on measures of pain, compared to Placebo TENS (P-TENS).

### 8.2: POWER CALCULATION:

---

The primary outcome measure was pain tolerance and from a review of the literature an accepted effect size was 0.8 (Roche et al 1984). A power calculation was performed to determine the sample size required to support statistical analysis at 80% power and a two-tailed 5% significance level. The study was powered to detect a large within-participant effect ( $\geq 0.8$ ; (Cohen 1988)) between the TENS and control using a repeated measures ANOVA. To detect such an effect with 80% power at a two-tailed 5% significance level, 16 participants were required in each of the two groups, giving an overall sample size of 32 participants.

### 8.3: METHOD:

---

#### 8.3.1: Design:

---

Initially, the study was designed as a repeated-measures experiment with each participant completing the experimental procedure on four occasions, experiencing all conditions: No-TENS, P-TENS, HF-TENS and LF-TENS. The university ethics committee did not feel that the possible outcomes of the research warranted this degree of participant involvement and thus advised that the design should be changed to minimise the burden on participants. Therefore, a single blind, placebo-controlled, repeated measures study design was selected as this maintained the benefits of the repeated measures design was proposed. The new design required participants to endure two episodes of induced pain rather than four. This new study design reduced the burden on the participants however it was not feasible to recruit enough participants required in the power calculation. This meant that the design restricted the evaluation of the effects of TENS. Rather than three TENS conditions (P-TENS, HF-TENS and LF-TENS) there was only enough time to recruit and compare two conditions. P-TENS was felt to be an essential component when investigating the effects of TENS. When consulting the literature around TENS and experimental ischaemic pain, HF-TENS was more often found to be the most effective mode and thus chosen for use in this study.

Ethical approval for the adjusted study design was obtained from the University Research Ethics Committee. The participants were randomised, using block randomisation, into either HF-TENS or P-TENS group. Each participant attended for one session that lasted approximately 2 hours where they completed two separate episodes of induced pain with the modified Submaximal Effort Tourniquet Test (mSETT). One mSETT was with no intervention (baseline) and the other with either P-TENS or HF-TENS intervention. The order of entry into the two study interventions was alternated. Fifty per cent of the participants in each group completed the baseline control condition followed by the TENS intervention (Figure 8.1).

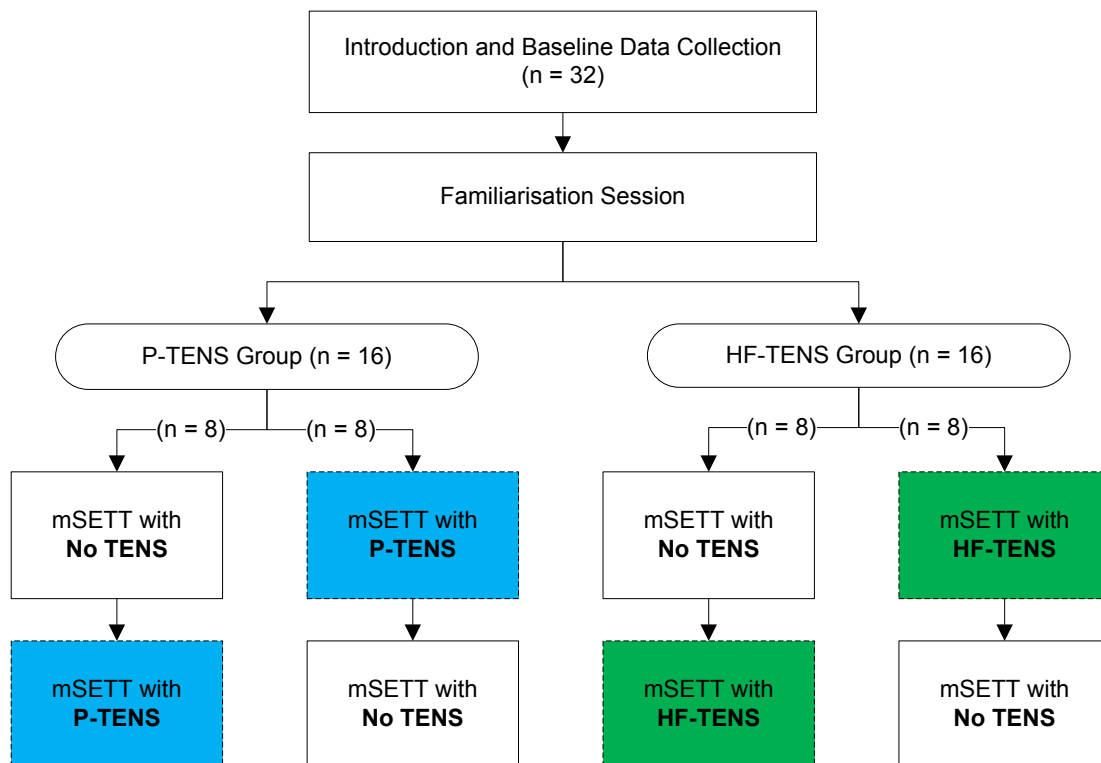


Figure 8.1: Flow diagram of participant study progression

### 8.3.2: Participants:

Prospective participants were recruited by email advertisement from the University's student population. Each participant received an information sheet (Appendix 4). Once each participant had read the information sheet and indicated that they were willing to take part in the study they were issued with an exclusion criteria questionnaire before providing written consent (Appendices 5 and 6). The exclusion criteria were reviewed at the testing session to ensure each participant understood the questionnaire and did not have any contraindications to electro stimulation and the mSETT. Participants were stratified by gender and then block-randomised to one of the two experimental groups.

### 8.3.3: Procedure:

The testing session followed the procedure as described in Chapter 7. However in this case the mSETT procedure was completed twice in the same testing session (Figure 8.1).



---

#### 8.3.4: TENS Procedure:

---

A standard, single-channel TENS machine was used for all sessions (NeuroTrac 3 <sup>™</sup>, Verity Medical Ltd, Surrey, UK). Placement sites were determined by the participant's report of where they experienced pain during the familiarisation mSETT. These sites were prepared using an Alcowipe (Universal Hospital Supplies Ltd, UK) and a standard sharp/blunt skin sensation test using single use sterile Neurotips (Owen Mumford Ltd, Woodstock, Oxford, UK). A segmental electrode application was employed using self-adhesive carbon rubber electrodes measuring 5x5cm (PhysioMed PALS<sup>®</sup> electrodes, Glossop, UK). Electrodes were attached to the TENS unit via dedicated manufacturer leads. The placement sites were commonly over the gastrocnemius muscle belly (Figure 8.2), at least 2cm apart. The superior electrode was positioned so that it covered the superior edge of the pain described and the inferior electrode similarly so that it covered the inferior edge of the area of pain. The electrodes once in place, were covered by the elastic bandage used for desanguination and remained in place throughout the experimental procedure (Figure 8.3).

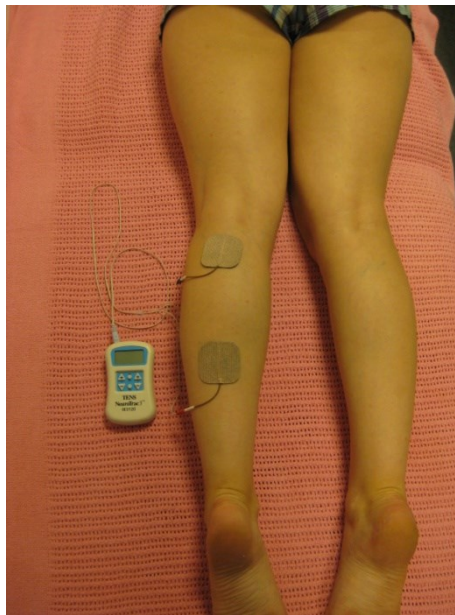


Figure 8.2: Common electrode placement sites with one electrode immediately superior and one immediately inferior to the Gastrocnemius muscle belly on the posterior aspect of the lower limb



Figure 8.3: The experimental set up including an example of the stimulation sites just visible beneath the elastic bandage

The TENS machine was a portable dual channel device with an asymmetrical biphasic waveform, which was calibrated prior to use using a digital recording oscilloscope and tested manually by the examiner prior to each testing session. The stimulation parameters were selected based on those commonly used in clinical practice and identified as efficacious in the TENS literature (Chen et al 2008). The TENS unit was calibrated to 120Hz, 200 $\mu$ s and patient determined intensity of “strong but comfortable”.

The Placebo stimulation was achieved using the same TENS unit and programmed settings. However, a different lead was used with an undecipherable break in the wires, covered by electrical tape (Figure 8.4).

This allowed the unit to be switched on and appear as if current was being applied but no current reached the participant. For the purpose of blinding, the participants were told that different dosages of TENS were being tested, some of which where the stimulation might not be perceivable even though the device is working (Roche et al 2002; Johnson and Tabasam 2003).



Figure 8.4: The wires used for HF-TENS and P-TENS stimulation

### 8.3.5: Measures:

Prior to the experiment, participants completed two questionnaires. Pain self-efficacy was measured using the Pain Self-Efficacy Questionnaire (PSEQ) (Nicholas 2007) and pain-related fear was measured using the Fear of Pain Questionnaire (FPQ) (McNeil and Rainwater III 1998). The scores on these questionnaires were used to establish baseline parity between the groups and thus help limit the effects of these psychosocial variables on the reporting of pain intensity between the groups.

Pain Threshold is defined as “the least experience of pain which a participant can recognise” (Merskey and Bogduk 1994). In the present study, it was defined to the participants as the time in seconds before “the moment discomfort turns to pain” and indicated by the participant saying, “pain now” (Melzack and Wall 1996; Roche et al 2002). Pain Tolerance is defined as “the greatest level of pain which a participant is prepared to tolerate” (Merskey and Bogduk 1994). For the purposes of the current study it was defined as the time in seconds before “the moment the participant reports that he/she is no longer able to tolerate the pain” and indicated by stating; “Stop” (Melzack and Wall 1996; Roche et al 2002). Pain Endurance was computed as the time in seconds between pain threshold and pain tolerance (Roche et al 2002).

Pain Intensity was measured using a 21-point Numerical Rating Scale (21-NRS): a numerical scale ranging from 0 to 20, with labels of “no pain” and “unbearable pain” respectively. The participant rated their pain at intervals using the 21-NRS, prompted by the audio track.

These ratings were at fixed, irregular intervals of 30, 35, 40, or 45 seconds. These intervals were irregular in sequence but the same in each test to allow comparison. The irregular intervals were used with the aim of blinding the participant to how long they had tolerated the pain. The recording asked them to “rate their pain on a scale of 0-20 where 0 represents no pain at all and 20 represents the point of unbearable pain”. The NRS has been found to be the superior method of rating pain intensity in terms of validity, reliability and practicality compared to VAS, box scales and verbal rating scales (Jensen et al 1986, Bolton and Wilkinson 1998). The use of 21 levels provides the optimum sensitivity to changes in pain intensity (Jensen et al 1994).

A McGill Pain Questionnaire (MPQ) was administered retrospectively, within 5 minutes of the participant reporting ‘pain tolerance’. The participant was asked to describe the pain they experienced at pain tolerance. The MPQ is valid and reliable in the laboratory setting (Klepac et al 1981) and can provide information regarding the pain qualities and intensity associated with different pain syndromes (Dubuisson and Melzack 1976; Jerome et al 1988; Katz and Melzack 1991; Dworkin et al 2009). Pain Rating Index (PRI) scores from the MPQ were recorded and analysed as a measure of the sensory, reactive and overall nature of the ischaemic pain at the point of tolerance (Melzack 1975; Roche et al 1984).

---

#### 8.3.6: Statistical Analysis:

---

All data are normally distributed and expressed as mean (standard error (SE)). A 2 x 2 factorial repeated measures Analysis of Variance (ANOVA) was used to analyse the data for time to pain threshold, tolerance and pain endurance. Factors were TENS type (2 levels, P-TENS/HF-TENS) entered as a between-subjects factor, and intervention (2 levels, no TENS/TENS intervention) entered as a within-subjects factor. Independent student’s t-tests and graphs of mean values were used to examine direction of effects.

Mean 21-NRS scores were analysed using a 2 x 18 factorial, repeated measures ANOVA to examine for any within-group effects of Intervention. Factors were intervention (2 levels, no TENS/TENS intervention) entered as a within subjects factor and time point (18 levels, every

NRS time point until all participants reached pain tolerance) entered also as a within-subjects factor. Between-subjects effects of TENS on pain intensity were analysed by calculating difference scores for 21-NRS (i.e. variation from baseline) for all participants as a method of standardising inter-participant variability (Foster et al 1996). To achieve this, participants 21-NRS score at baseline was subtracted from that with HF-TENS or P-TENS for each time point during the mSETT. Group means of these difference scores are presented in graphical format and analysed using a one-way ANOVA.

Pain Quality, measured by the PRI of the MPQ, was also analysed using a 2 x 2 factorial, repeated measures ANOVA. Again, time point (2 levels, pre/post intervention) was entered as a within-subjects factor and group (2 levels, P-TENS/HF-TENS) as a between-subjects factor. The full analysis plan is detailed in Figure 8.5 to aid clarity.

Statistical significance was set at  $p = 0.05$  (two-tailed). Analysis was performed using SPSS version 19.0.

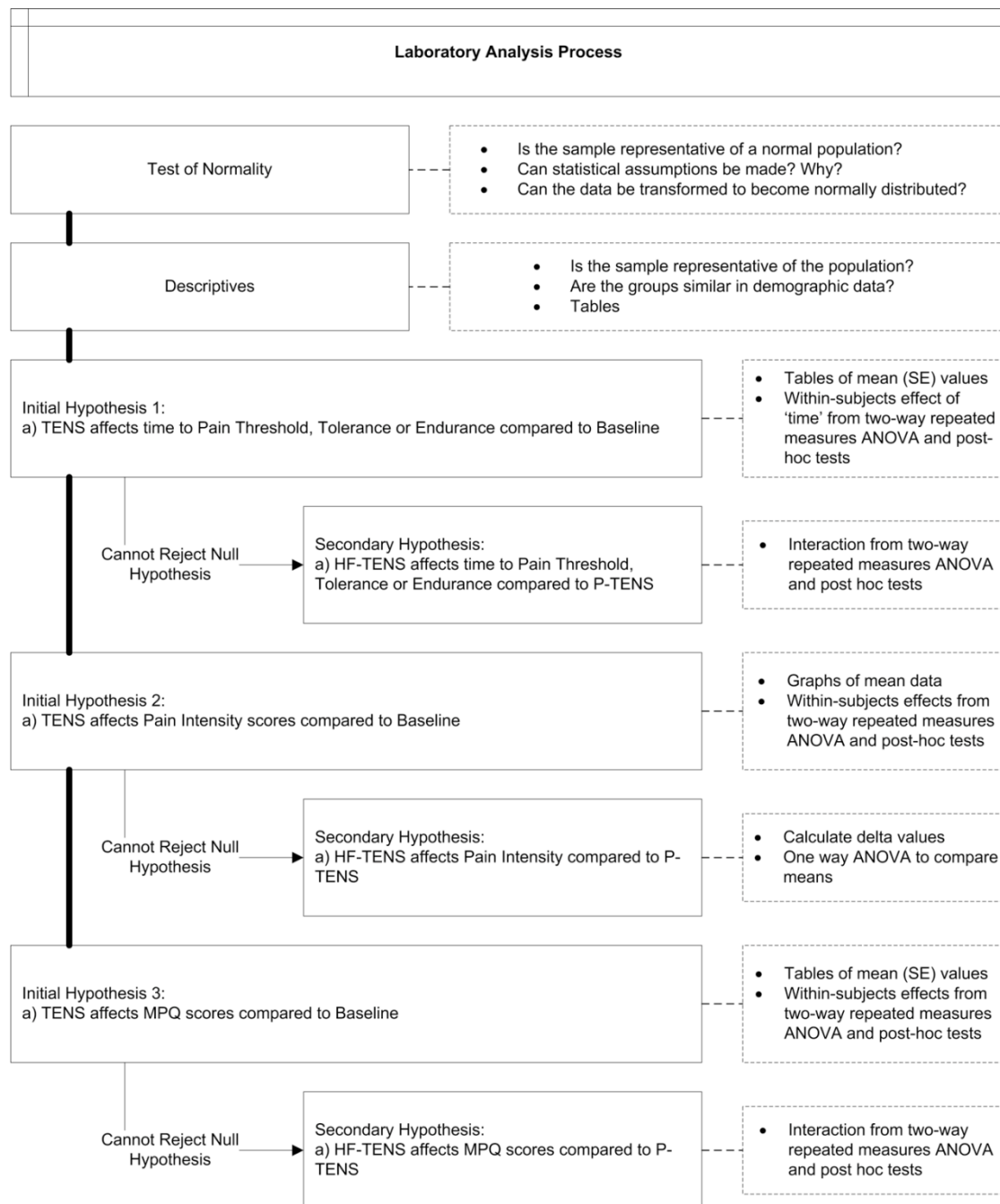


Figure 8.5: Summary of data analysis plan

## 8.4: RESULTS:

The participants were 32 healthy volunteers (18 male, mean age 28 years, range 19-47) without previous experience of TENS or any known pathology that could cause pain. During testing, 1 participant dropped out and 4 were excluded from analysis. The dropout was due to not wishing to continue with the experiment and the exclusions from analysis were due to not understanding and completing the experimental instructions correctly. Two participants were from the P-TENS group and no further volunteers were recruited. Figure 8.6 summarises this information and displays the progress of participants through the study.

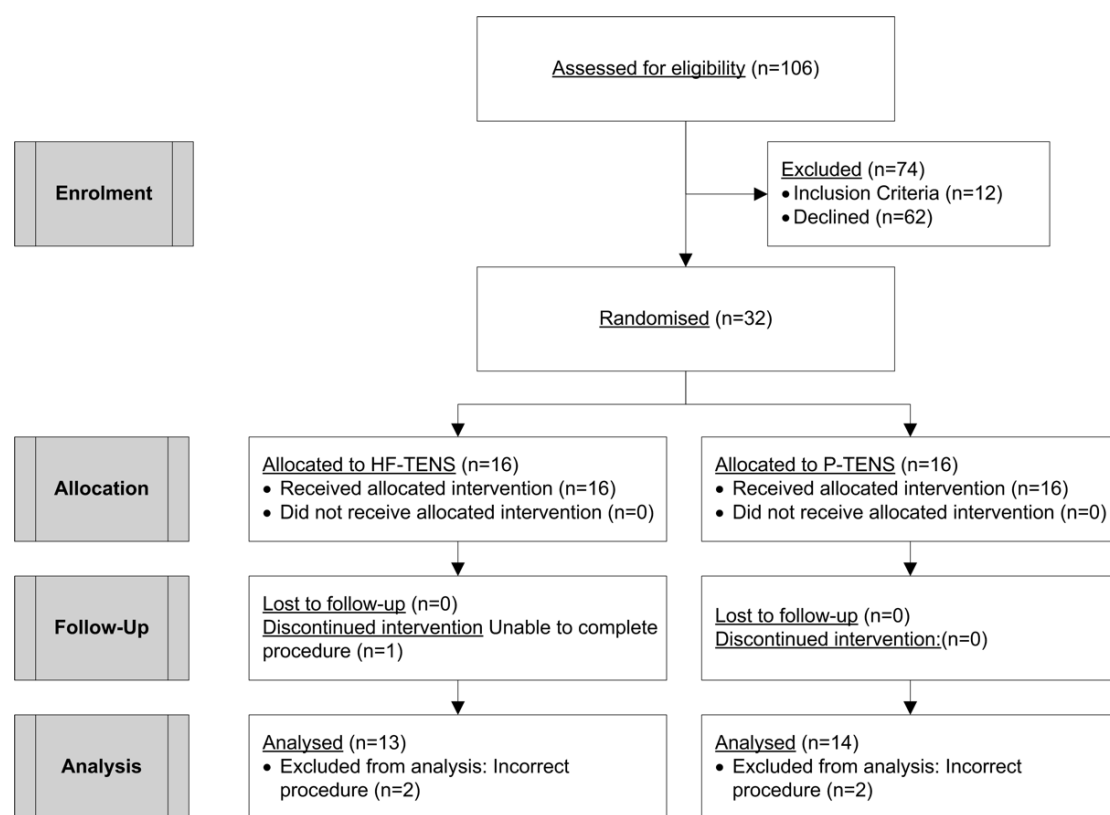


Figure 8.6: CONSORT diagram displaying the progression of participants through the study.

A total of 27 healthy volunteers were included in the analysis (16 male; mean age 27 years, range 19-47). Groups were similar in terms of demographic data, psychosocial measures and baseline reports of pain (Table 8.1).

Table 8.1: Mean (SE) baseline data for all participants. *p* value represents result of independent student's t-test (two-tailed).

	All Participants	Group		<i>p</i> value
		P-TENS	HF-TENS	
<b>Age (years)</b>	26.9 (1.14)	25.5 (0.97)	28.2 (1.99)	0.242
<b>BMI (kg/m<sup>2</sup>)</b>	24.1 (0.49)	23.9 (0.66)	24.3 (0.75)	0.702
<b>HR (bpm)</b>	67.9 (1.66)	67.0 (2.29)	68.9 (2.45)	0.586
<b>BP (sys) (mmHg)</b>	121.5 (1.47)	120.2 (2.22)	122.6 (1.97)	0.423
<b>PSEQ</b>	21.0 (2.27)	19.5 (3.32)	22.4 (3.18)	0.535
<b>FPQ</b>	85.37 (3.70)	87.4 (7.27)	83.50 (2.65)	0.623
<b>Pain Threshold (secs)</b>	125.4 (4.61)	129.0 (6.22)	122.1 (6.86)	0.635
<b>Pain Tolerance (secs)</b>	396.3 (16.36)	407.5 (26.30)	386.0 (20.55)	0.299
<b>Pain Endurance (secs)</b>	270.9 (14.73)	278.5 (24.82)	263.9 (17.36)	0.310

#### 8.4.1: Pain Intensity:

##### 8.4.1.1: Pain Threshold, Tolerance and Endurance:

Table 8.2 details the time taken for participants to report pain threshold and pain tolerance and the calculated pain endurance in both groups. These measures are shown with no intervention (baseline) and with TENS intervention.

Table 8.2: Mean (SE) time (secs) to pain threshold, pain tolerance and pain endurance for both groups with TENS and with no intervention (baseline)

		Baseline	Intervention
<b>P-TENS Group</b>	<b>Pain Threshold</b>	129.0 (6.2)	132.9 (5.8)
	<b>Pain Tolerance</b>	407.5 (26.3)	450.9 (27.8)
	<b>Pain Endurance</b>	278.5 (24.8)	318.1 (25.7)
<b>HF-TENS Group</b>	<b>Pain Threshold</b>	122.1 (6.9)	151.4 (8.9)
	<b>Pain Tolerance</b>	386.0 (20.6)	585.0 (30.4)
	<b>Pain Endurance</b>	263.9 (17.4)	433.6 (24.5)



A two-way Analysis of Variance (ANOVA) was conducted to examine the effect of intervention (no TENS versus TENS) and TENS type (P-TENS versus HF-TENS) on the measures of pain threshold, tolerance and endurance.

The dependant variables were normally distributed for the groups formed by the combination of the intervention and TENS type as assessed by the Shapiro-Wilk test. There was homogeneity of variance between groups as assessed by Levene's test for equality of error variances. Results are reported with a measure of effect size, partial eta-squared ( $\eta_p^2$ ).

A significant effect of intervention was observed for time to pain threshold ( $F(1,25) = 16.304, p < 0.001, \eta_p^2 = .395$ ), time to pain tolerance ( $F(1,25) = 37.681, p < 0.001, \eta_p^2 = .601$ ) and pain endurance time ( $F(1,25) = 33.166, p < 0.001, \eta_p^2 = .570$ ) (Figures 8.7-8.9). This indicates that these measures of pain intensity change with TENS intervention (P-TENS and/or HF-TENS).

The interaction between intervention and TENS type was found to be significant for time to pain threshold ( $F(1,2) = 6.865, p = 0.015, \eta_p^2 = .215$ ), time to pain tolerance ( $F(1,25) = 14.586, p = 0.001, \eta_p^2 = .368$ ) and pain endurance ( $F(1,25) = 12.662, p = 0.002, \eta_p^2 = .336$ ) (Figures 8.7-8.9). This indicates that one group changed over time to a greater extent than the other for each measure. No significant effects were found for TENS type alone.

Independent student's t-tests examining for differences between the groups found no difference at baseline or with intervention for time to pain threshold. Significant differences were found between groups with intervention for time to pain tolerance and endurance ( $t(25) = -2.891, p = 0.008, r = 0.50$  and  $t(25) = -2.867, p = 0.008, r = .50$  respectively).

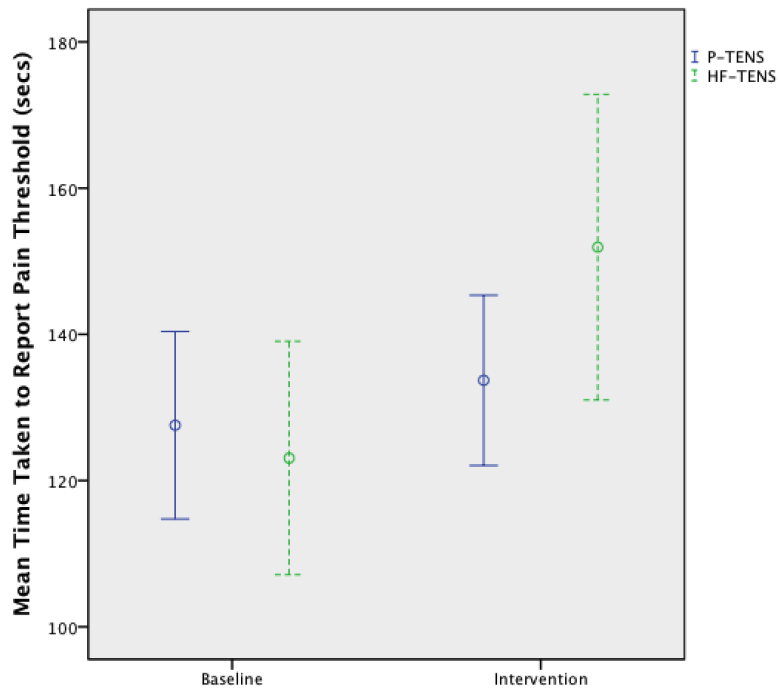


Figure 8.7: Mean time taken to report pain threshold at baseline and with intervention in both groups. Change from baseline with intervention was significant for both groups. Error bars represent 95% confidence intervals.

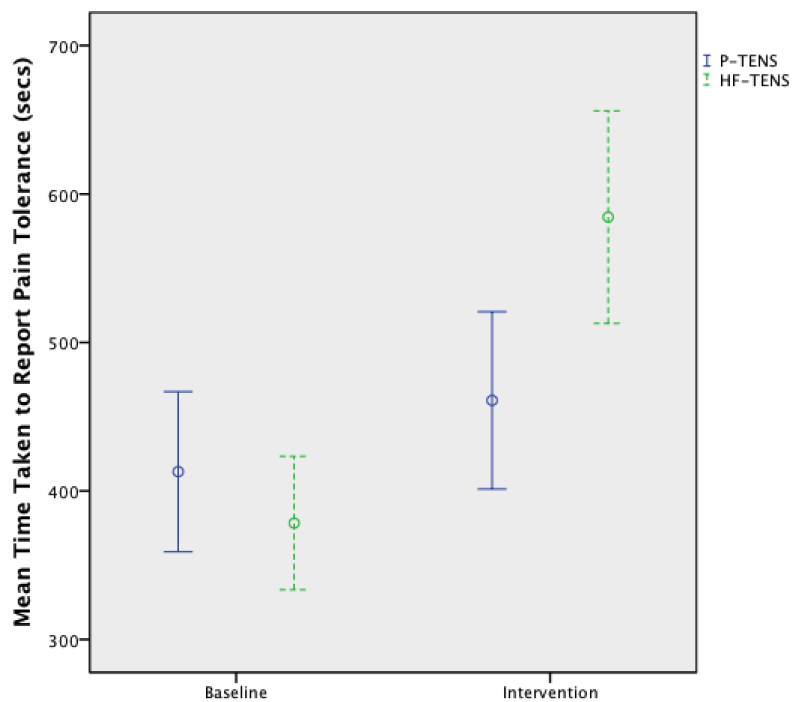


Figure 8.8: Mean time taken to report pain tolerance at baseline and with intervention in both groups. Change from baseline with intervention was significant for both groups. However, change with HF-TENS was greater than that with P-TENS. Error bars represent 95% confidence intervals.

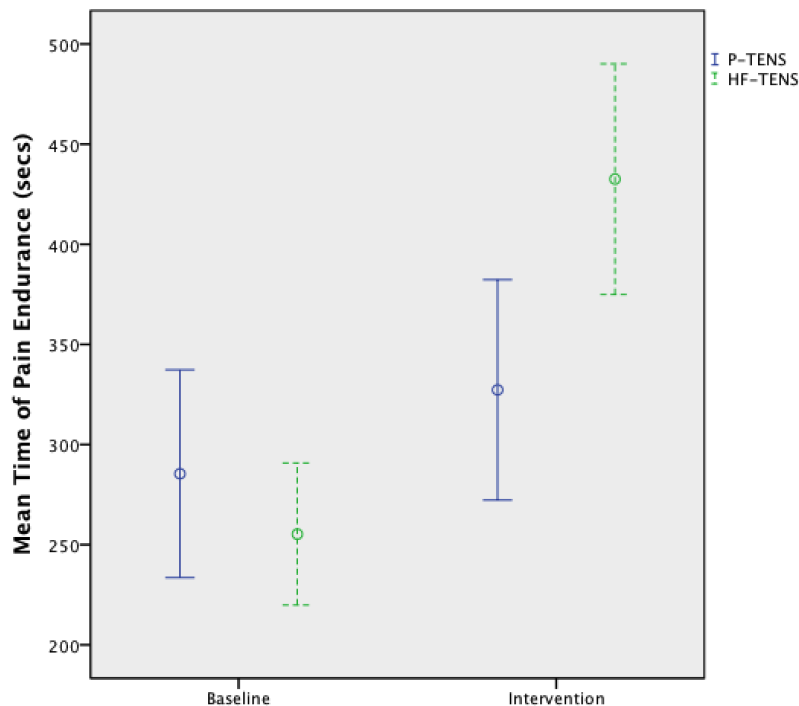


Figure 8.9: Mean pain endurance at baseline and with intervention in both groups. Change from baseline with intervention was significant for both groups. However, change with HF-TENS was greater than that with P-TENS. Error bars represent 95% confidence intervals.

#### 8.4.1.2: 21-NRS Scores:

Figures 8.10-12 display the 21-NRS scores recorded during the mSETT. Mean scores are shown for both groups at baseline (Figure 8.10), with intervention (Figure 8.11) and the mean difference scores (Figure 8.12). A common pattern of increasing pain intensity over time was observed in both groups with no intervention (Figure 8.10). All participants reached pain tolerance by time point 12 (9 minutes). There were no differences between the groups at any time point.

Figure 8.11 details the mean pain intensity with HF-TENS and P-TENS interventions. All participants in the P-TENS group had reached pain tolerance by 11 minutes and all participants in the HF-TENS group had reached pain tolerance by 13 minutes (Figure 8.11). Mean scores at each time point were compared with baseline using one-way, repeated measures ANOVA. For P-TENS, no differences between the reported pain intensity were

found. Mean 21-NRS scores were significantly reduced with HF-TENS however from the 6<sup>th</sup> to the 10<sup>th</sup> minutes ( $p < .05$ ).

Both HF-TENS and P-TENS groups showed a mean reduction in pain intensity, as indicated by the negative values in Figure 8.12. Apart from the 3<sup>rd</sup> minute, participants in the HF-TENS group reported a greater reduction throughout pain duration compared with P-TENS. Scores with HF-TENS intervention were significantly lower in the 4<sup>th</sup> minute and from the 6<sup>th</sup> to the 9<sup>th</sup> minute (one-way ANOVA for individual change from baseline at each time point) (Figure 8.12).

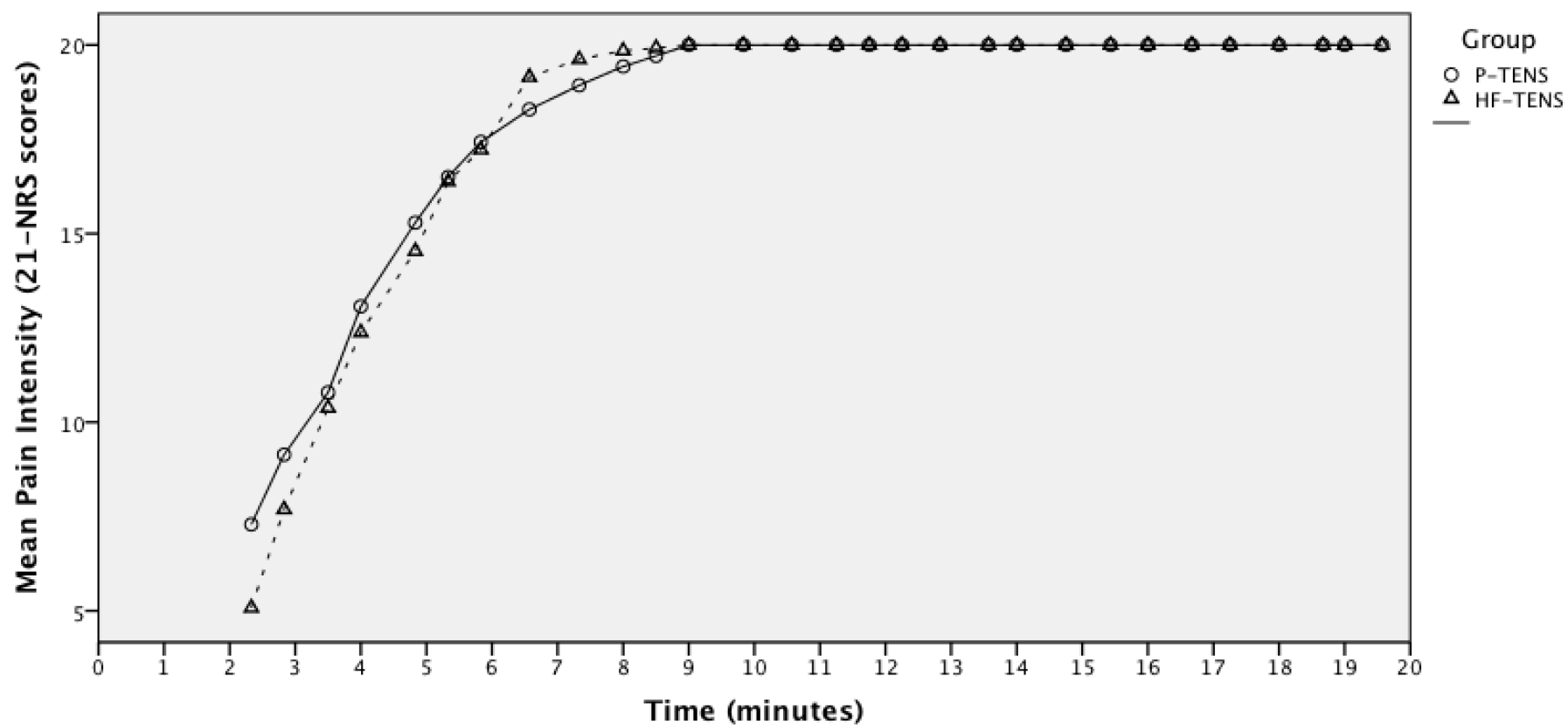


Figure 8.10: Mean 21-NRS scores during baseline mSETT with no intervention. There were no differences between the groups at any time point.

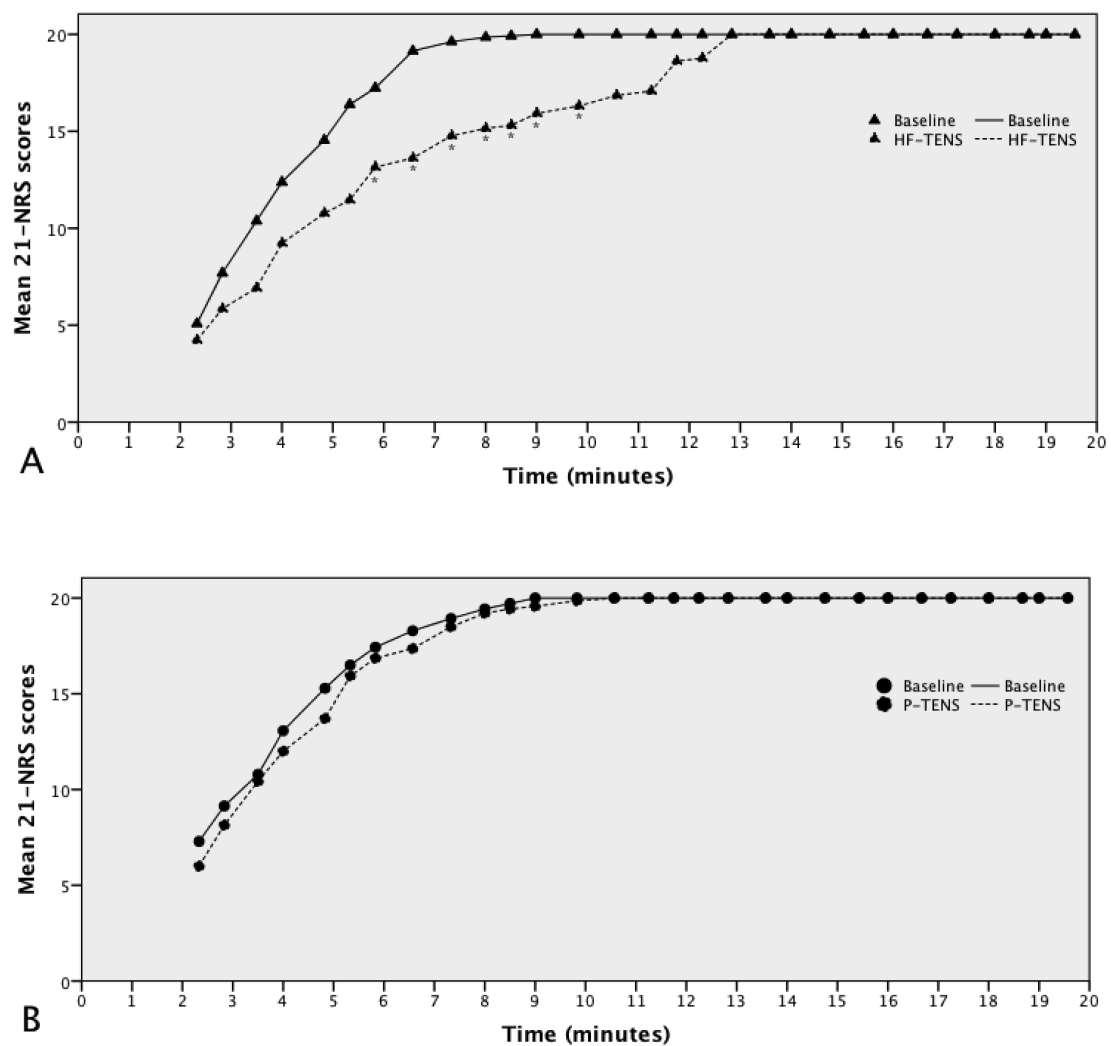


Figure 8.11: Mean 21-NRS scores during intervention mSETT in A) the HF-TENS and B) the P-TENS groups. No significant changes from baseline were observed at any point in the P-TENS group. Mean 21-NRS scores were significantly lower than baseline from minute 6 to 10 in the HF-TENS group (\*  $p < .05$ , one way repeated measure ANOVA).

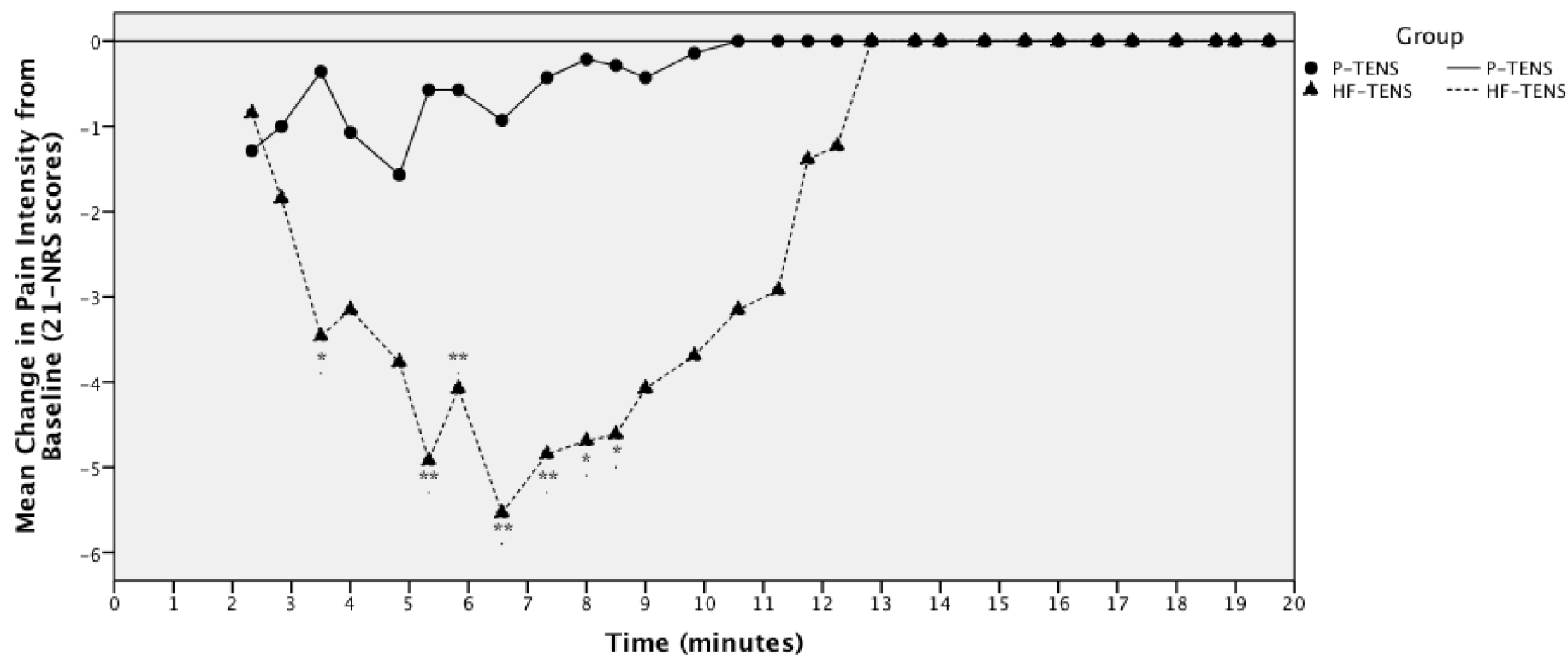


Figure 8.12: Mean individual change in 21-NRS scores throughout the mSETT in both groups. Change with HF-TENS was greater than with P-TENS in the 4<sup>th</sup> minute and then from the 6<sup>th</sup> to the 9<sup>th</sup> minute. Significant differences between groups indicated by \*  $p < 0.05$ ; \*\*  $p < 0.01$ , one-way ANOVA.

#### 8.4.2: Pain Quality:

Table 8.3 details the Total PRI (TPRI), Sensory PRI (SPRI) and Reactive PRI (RPRI) scores in the P-TENS and HF-TENS groups. PRI scores are shown with no intervention (Baseline) and with TENS intervention (TENS).

Table 8.3: Mean (SE) PRI scores for both groups with placebo and with TENS intervention.

		Baseline	TENS
<b>P-TENS Group</b>	<b>TPRI</b>	27.4 (2.2)	23.2 (1.8)
	<b>SPRI</b>	15.9 (1.3)	13.4 (1.0)
	<b>RPRI</b>	11.5 (1.1)	9.80 (1.0)
<b>HF-TENS Group</b>	<b>TPRI</b>	30.9 (3.2)	24.6 (2.9)
	<b>SPRI</b>	19.2 (1.7)	15.1 (1.8)
	<b>RPRI</b>	11.7 (1.7)	9.50 (1.4)

A two-way ANOVA was conducted that examined the effect of intervention (no TENS versus TENS) and TENS type (P-TENS/HF-TENS) on PRI scores. The dependent variable, PRI score, was normally distributed for the groups formed by the combination of the intervention and TENS type as assessed by the Shapiro-Wilk test. There was homogeneity of variance between groups as assessed by Levene's test for equality of error variances. Results are reported with a measure of effect size, partial eta-squared ( $\eta_p^2$ ).

A significant effect of intervention was observed for TPRI scores ( $F(1,25) = 11.829$ ,  $p = 0.002$ ,  $\eta_p^2 = .321$ ), SPRI scores ( $F(1,25) = 10.644$ ,  $p = 0.003$ ,  $\eta_p^2 = .299$ ) and RPRI scores ( $F(1,25) = 6.871$ ,  $p = 0.015$ ,  $\eta_p^2 = .216$ ). This indicates that all PRI scores changed over time with TENS intervention (P- and/or HF-TENS).

No significant effects were found for the interaction of intervention and TENS type of TPRI, SPRI or RPRI scores ( $F(1,25) = 0.223$ ,  $p = 0.641$ ,  $\eta_p^2 = .009$ ;  $F(1,25) = 0.896$ ,  $p = 0.353$ ,  $\eta_p^2 = .035$  and  $F(1,25) = 0.038$ ,  $p = 0.847$ ,  $\eta_p^2 = .002$  respectively). These results indicate that neither group changed over time to a greater extent than the other. No significant effect of



TENS type on TPRI, SPRI or RPRI was found ( $F(1,25) = 0.729, p = 0.401, \eta_p^2 = .028$ ;  $F(1,25) = 1.714, p = 0.202, \eta_p^2 = .064$  and  $F(1,25) = 0.053, p = 0.820, \eta_p^2 = .002$  respectively).

Figures 8.13-15 display the mean PRI scores in both groups over time. TPRI scores with intervention (HF and P-TENS) were lower than at baseline (mean difference, 5.55; 95% CI, 2.23-8.87;  $p = 0.002$ ) (Figure 8.13). The same was true for SPRI (mean difference, 3.22; 95% CI, 1.19-5.25;  $p = 0.003$ ) and RPRI (mean difference, 2.33; 95% CI, 0.50-4.16;  $p = 0.015$ ) (Figures 8.14 and 8.15).

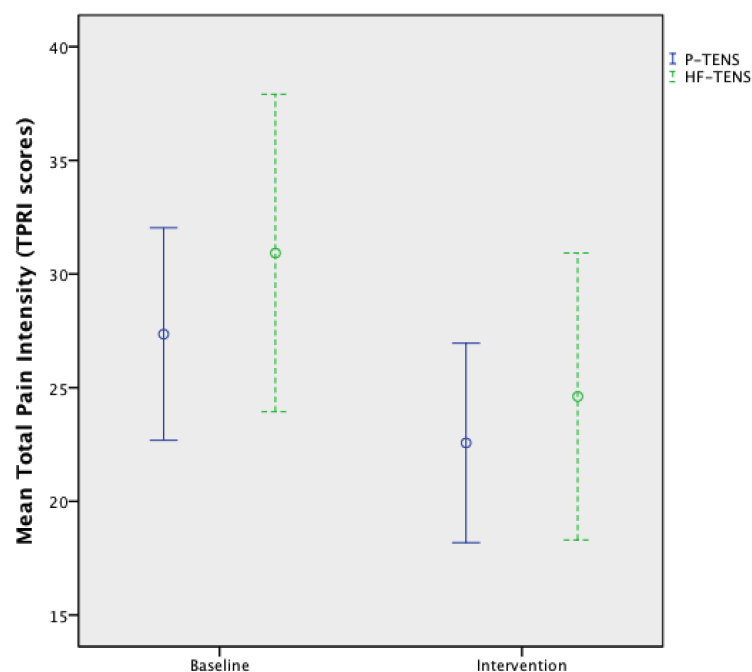


Figure 8.13: Mean TPRI scores at baseline and with intervention in both groups. Change from baseline with intervention was significant for both groups. No differences were found between the groups (two-way repeated measures ANOVA). Error bars represent 95% confidence intervals.

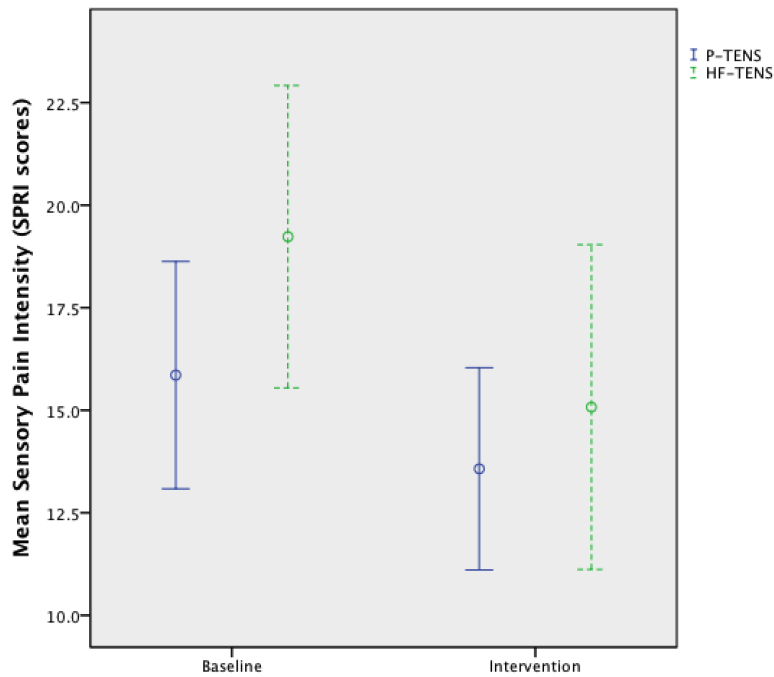


Figure 8.14: Mean SPRI scores at baseline and with intervention in both groups. Change from baseline with intervention was significant for both groups. No differences were found between the groups (two-way repeated measures ANOVA). Error bars represent 95% confidence intervals.

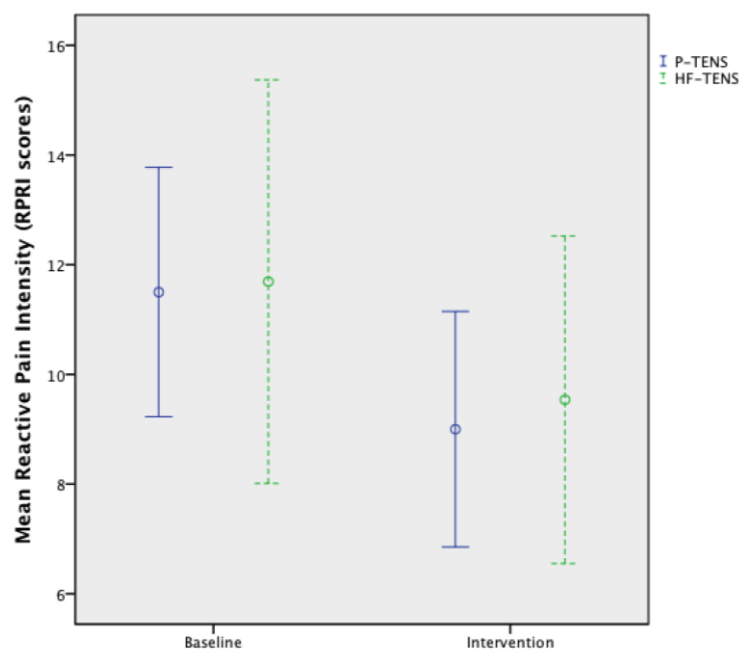


Figure 8.15: Mean RPRI scores at baseline and with intervention in both groups. Change from baseline with intervention was significant for both groups. No differences were found between the groups (two-way repeated measures ANOVA). Error bars represent 95% confidence intervals.

## 8.5: DISCUSSION:

---

This experiment used a novel mSETT methodology to induce ischaemic pain in the lower limb. The results indicate that both High Frequency TENS (HF-TENS) and Placebo TENS (P-TENS) reduced pain compared to no intervention. However, when compared to P-TENS, HF-TENS delayed pain perception and pain tolerance for longer; and lowered pain levels to a greater extent, over a longer period of time. HF-TENS therefore had a greater impact on several aspects of the mSETT-induced pain experience than P-TENS.

HF-TENS is proposed to act by activating large diameter mechanoreceptors ( $A\beta$ -fibres), delta ( $\delta$ )-opioid receptors and increasing gamma-Aminobutyric acid (GABA) in the dorsal horn of the spinal cord (Sluka and Walsh 2003; DeSantana et al 2008; Chen and Johnson 2011). This mechanism of action is associated with immediate, localised, segmental inhibition as conceived by the original gate control theory (Melzack and Wall 1965; Andersson 1979; Sluka and Walsh 2003). It is these mechanisms that appear to explain the hypoalgesic effects of HF-TENS observed in this study. As highlighted in Figure 8.7, HF-TENS had an immediate effect. The mean delay in the initial perception of pain in the HF-TENS group was 29.3 seconds, representing a 24% increase from baseline. Once pain was perceived, HF-TENS reduced the severity of the pain and increased the time it took participants to reach and report pain tolerance by an average of 199.0 seconds, an increase of 52% compared to baseline. The effect of the delay in pain threshold and pain tolerance, and the reduction of pain intensity between these two points, was to extend pain endurance by 163.7 seconds i.e. 64% longer than baseline. These data, as shown in Figures 8.7-9, indicate an inhibition of the perception of pain initially at pain threshold, during the minute-by minute endurance of pain, and at the point of pain tolerance i.e. at three key points across the induced ischaemic pain experience in volunteers.

Figure 8.10 represents the level of pain being experienced without any intervention. Lower limb induced ischaemic pain increased steadily and gradually over time, in both groups. When interventions were applied (Figure 8.11 and 12), the P-TENS group reported mild reductions in mean pain scores throughout the period of induced pain. In contrast, HF-TENS

showed a more extreme dip and longer lasting reduction of mean pain scores over time. The reduction of mean pain intensity with HF-TENS was significantly lower than that with placebo at seven points throughout the pain experience. Furthermore, as shown in Figures 8.10 and 12, the reduction in mean pain scores with HF-TENS was greatest when pain intensity would normally have reached its highest levels had TENS not been applied i.e. from the 6<sup>th</sup> to the 9<sup>th</sup> minutes. These results suggest that spinal gating inhibition is strong over a relatively short period. It is nevertheless gradually overcome when there is on-going nociceptive input, in this case from cuff-induced ischaemia, occurring over an average pain endurance of  $432.5 \pm 26.4$  seconds (approximately 7 minutes) (Figures 8.11 and 8.12).

Table 8.3 shows the mean MPQ scores of intolerable pain reported retrospectively by participants completing their Baseline and TENS trials. Significant reductions in Sensory pain from HF-TENS, and in Sensory and Reactive pain from P-TENS contributed to significantly lower Total MPQ scores of intolerable pain in both groups (Table 8.3 and Figures 8.13-15). The application of both a placebo and active TENS (HF-TENS) appears to have lowered the level of participants' tolerance for pain. Figure 8.12 shows that pain intensity was modified in both HF-TENS and P-TENS conditions during the first two-thirds of the period of pain endurance. The pain returned however to higher levels during the latter one-third. In the case of HF-TENS, there was resurgence in pain intensity over the latter 2-3 minutes. This suggests that the TENS-induced inhibition ceased to be effective. Participants in the HF-TENS condition may have found the resurgence of pain following a period of relatively mild pain to be intolerable, sooner than was the case in their baseline condition. Only sensory pain scores were significantly reduced in the HF-TENS condition resulting in significant reduction in the HF-TENS Total PRI (Table 8.3). This result suggests that pain reduction with HF-TENS was founded on a reduction in sensory perception of noxious input, supporting the hypothesis of spinal and/or peripheral inhibition.

Participants in the P-TENS group experienced considerably less of a drop, and resurgence, of pain than did the HF-TENS group. P-TENS pain levels dipped only slightly over the first 6 minutes of ischaemic pain. They then remained at the same level for several minutes, a level

that was reported as intolerable (Figure 8.12). It was suggested to participants with P-TENS that they were being given a real treatment for their pain. The significant reduction in both their Sensory and Reactive MPQ scores with P-TENS suggest a significant placebo effect, involving psychologically driven, physiological mechanisms of pain relief (Roche et al 1984; Amanzio and Benedetti 1999; Amanzio et al 2001; Roche et al 2002). Both sensory and reactive pain scores from the MPQ were reduced with P-TENS. This resulted in an overall reduction in PRI scores and supports the psychologically driven physiological mechanisms of placebo hypoalgesia (Amanzio et al 2001).

Overall, the results suggest that both physiological and psychological mechanisms of pain inhibition were activated by the application of TENS in this laboratory study. However, HF-TENS was found to be more effective.

The results of this experimental study using mSETT are in line with the previous results indicating delayed perception of pain and modified pain scores in induced lower limb ischaemic pain (Roche et al 2007). The effect of HF-TENS on the mSETT method therefore appears to be replicable using this methodology. Furthermore, HF-TENS in both upper limb and lower limb induced ischaemic pain, delays pain tolerance (Woolf 1979; Roche et al 1984) and decreases pain intensity as measured with linear pain scales (Woolf 1979; Roche et al 1984; Johnson and Tabasam 2003; Chen and Johnson 2011). A recent study (Chen and Johnson 2011) showed that HF-TENS (vs. LF and Placebo TENS) reduced pain intensity during the first 2 minutes of induced upper limb ischaemic pain. This study is the first to report results of TENS on lower limb induced ischaemic pain and it shows initial and extending reductions of pain intensity over several more minutes than do Chen and Johnson (2011) for upper limb pain. These results, shown over approximately 12 minutes of testing suggest a potential utility of TENS for clinical ischaemic pain in the lower limb.

## 8.6: CONCLUSIONS:

---

The modified Submaximal Effort Tourniquet Test (mSETT), used to induce lower limb ischaemic pain gave a detailed picture of the ischaemic pain curve, and its inhibition in

healthy volunteers. HF-TENS modified three key aspects of the ischaemic pain experience over time: pain threshold, pain tolerance and pain endurance. HF-TENS also reduced pain intensity measured with a numerical pain scale during ischaemia. Interestingly it also lowered the psychological point at which participants reported pain intolerance as measured with an MPQ. This preliminary study on lower limb induced ischaemia showed that HF-TENS had both physiological and psychological effects.

#### 8.7: CHAPTER 8 SUMMARY:

---

TENS is a possibly useful, yet untested adjunctive intervention for IC pain. Prior to investigation in clinical populations, it is important to study the effects of TENS on a pre-clinical model of IC pain. The mSETT has been developed to possibly fulfil this role as it induces ischaemic pain in the lower limb of healthy volunteers. The aim of this chapter was to describe the investigation of TENS for pain induced by the mSETT.

HF and P-TENS were applied to the calf of volunteers undergoing the mSETT. Both applications of TENS were found to increase the time taken to report pain threshold, pain tolerance and pain endurance. There was no difference between the interventions for time to pain threshold but HF-TENS was found to increase time to pain tolerance and endurance greater than P-TENS. HF-TENS was also found to decrease pain intensity to a greater extent than P-TENS between the 3<sup>rd</sup> to the 9<sup>th</sup> minutes.

These findings indicate that TENS is effective at reducing laboratory-induced, lower limb ischaemic pain. This finding adds weight to the proposition that TENS may be an effective intervention for IC pain. The next chapter examines this proposition by investigating the effects of TENS in a clinical population with IC pain.

## CHAPTER 9: EXPERIMENT THREE - THE EFFECTS OF TENS ON PAIN AND WALKING PERFORMANCE IN PATIENTS WITH PAD AND IC

---

### 9.1: AIM OF CHAPTER 9:

---

A aim of this thesis is to investigate the hypoalgesic effects of TENS on lower limb ischaemic pain and walking performance in patients with IC. Chapters 7 and 8 have established a reliable method for inducing ischaemic pain in the lower limb of healthy volunteers and examined the hypoalgesic effects of TENS on this induced pain. These studies form the important pre-clinical investigation of TENS as a possible intervention for IC and TENS has been found to have hypoalgesic effects on ischaemic pain induced in the laboratory.

Prior to being confirmed as a useful clinical intervention for patients with PAD and IC, the effects of TENS on clinical IC pain must be examined. Also, the potential for the main different types of TENS to maximally affect pain and function must be investigated. This chapter aims to describe a pilot investigation of the effects of two different stimulation patterns of TENS on measures of pain and walking performance in patients with PAD and IC.

### 9.2: POWER CALCULATION:

---

As this was designed as a MRC phase IIa, 'proof of concept' trial, the sample size was set prior to the power calculation. The sample size of 40 participants in two groups (20 per group) at 80% power and a two-tailed 5% significance level could detect a large effect ( $\geq 0.8$ ; (Cohen 1988)) between each of the TENS groups and placebo TENS control group using repeated measures ANOVA.

---

#### 9.2.1: Clinically Significant Difference:

---

A 60% improvement in ACD has been quoted as a worthwhile improvement in walking distance (Oakley et al 2008). As TENS has not been tested on IC pain, there is no evidence that it may achieve this worthwhile increase. However, in laboratory studies of the effects of TENS on experimentally induced ischaemic pain, a 50-70% reduction in time to pain threshold and pain tolerance has been demonstrated (Roche et al 1984; Chen and Johnson

2011). If this effect of TENS on experimental ischaemic pain transfers to an improvement in walking performance in the clinical population, it will be a worthwhile intervention.

---

### 9.3: METHODS:

---

#### 9.3.1: Design:

---

Ethical approval for the study was obtained from the local National Health Service Research Ethics Committee (Tayside Committee on Medical Research Ethics B). The study design is an experimental, patient-concealment, placebo-controlled, MRC phase IIa, 'proof-of-concept' trial. The participants were randomised, using block randomisation, into either HF-TENS or LF-TENS group (Appendix 7). Each participant attended for two sessions at least 24 hours apart and lasting approximately two hours each time. A treadmill protocol (Gardner et al 1991) was completed by the participant at each session, the first with the TENS intervention and secondly with P-TENS (Figure 9.1). The order of the sessions was not randomised because of the training effect of the treadmill test (Gardner et al 1991). In the current study, the active TENS condition was conducted first so that any increase in walking distance compared to P-TENS condition might be attributed to TENS.

---

#### 9.3.2: Participants:

---

Prospective participants with stable PAD and IC, who met the study inclusion and exclusion criteria, were recruited from the vascular outpatient clinic at Ninewells Hospital, Dundee. Each participant received an information sheet and 'opt-in' slip (Appendix 8). If they were willing to take part in the study, they returned the 'opt-in' slip and were contacted to arrange the testing sessions. At the first testing session, the exclusion criteria were reviewed with the participant before providing written consent (Appendix 9). Figure 9.2 displays the common clinical journey of patients with PAD and IC and the relationship with the current study procedures.



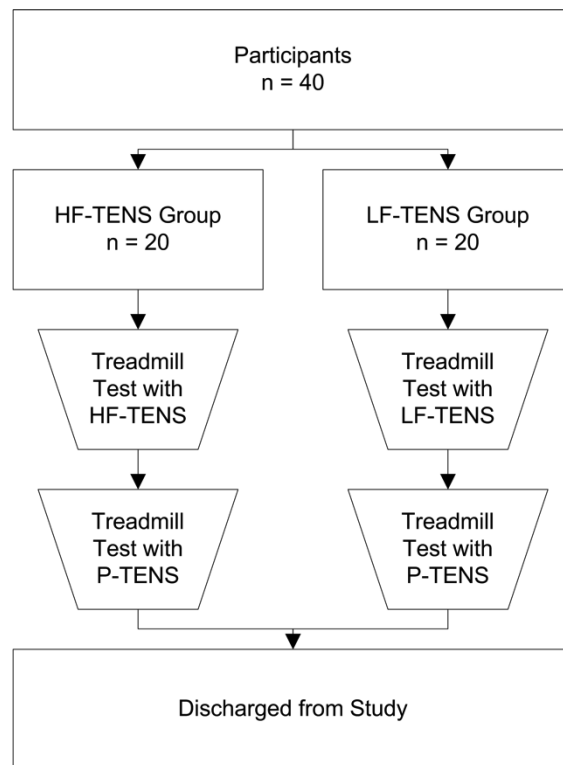


Figure 9.1: Order of intervention for each group.

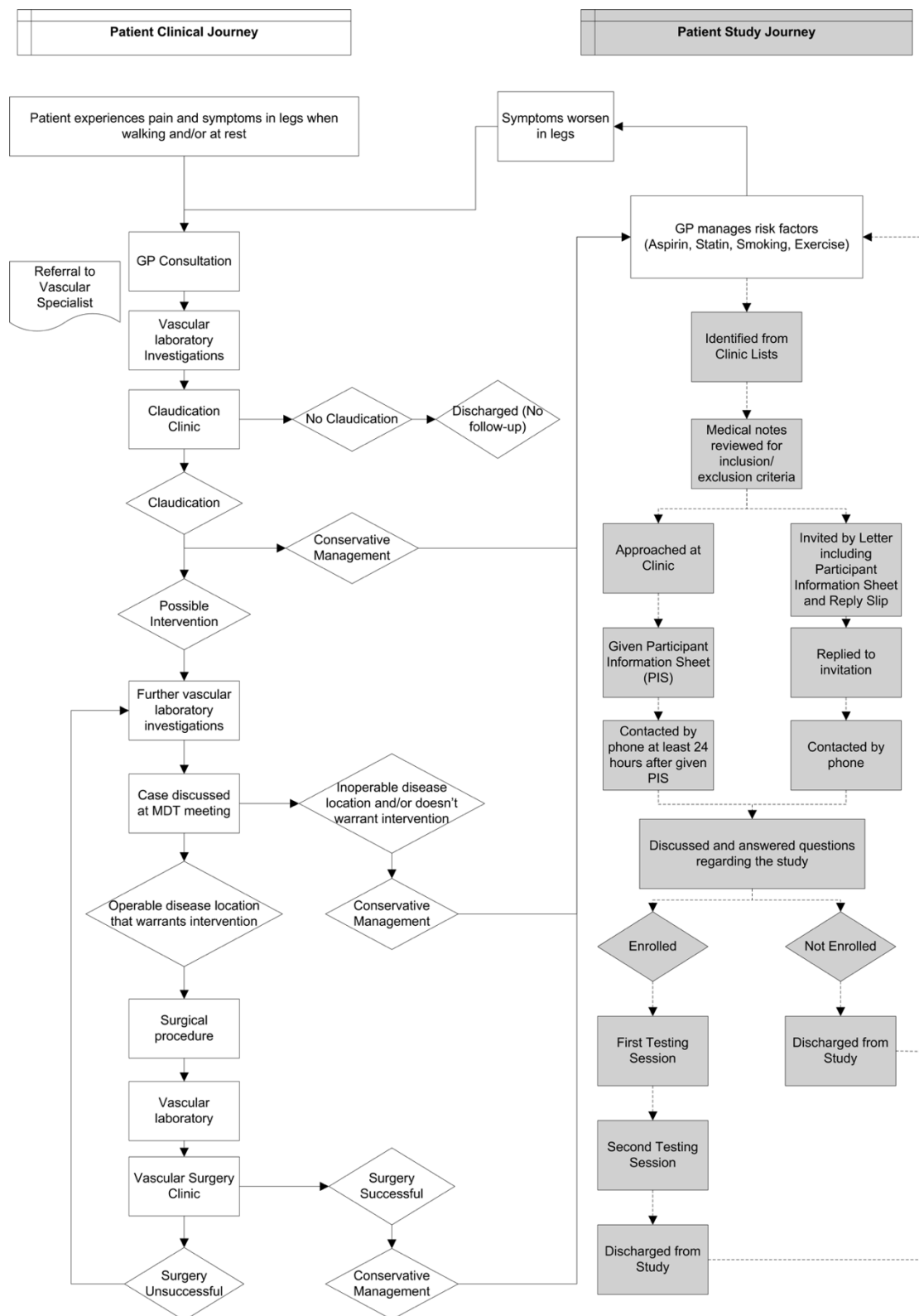


Figure 9.2: A flow diagram illustrating the relationship between the normal patient journey and that of the current study. The normal clinical journey of a patient with PAD and IC at the centre where the study participants were recruited is shown on the left. In grey, the current study journey.

### 9.3.2.1: Inclusion and Exclusion Criteria:

---

The inclusion and exclusion criteria reflect that used currently in the TENS and PAD literature and helps to ensure the safety of the participants in the study (McDermott et al 2009; Chen and Johnson 2011).

#### Inclusion:

- Clinical diagnosis of PAD and stable IC of more than 3 months duration
- Fontaine stage II
- Resting ABPI less than 0.90 in at least one leg
- Walking limited only by claudication
- Independent and safe mobility (no walking aids)
- Cognitively stable and able to follow instruction (MSQ 10/10, MMSE 30/30)

#### Exclusion:

- Less than 40 years of age
- Planned surgical or endovascular intervention for PAD
- Any leg ulceration
- Any Exercise-limiting co-morbidities e.g. congestive cardiac failure, angina, dyspnoea, MSK or neurological impairment
- Co-morbidities causing pain in the lower limb
- Ataxic gait or history of increased falls (unsafe for treadmill walking)
- MI  $\leq$  6 months ago, Cardiac arrhythmia or Cardiac pacemaker
- Current or previous sensation abnormalities in the lower limbs e.g. severe peripheral neuropathies
- Cognitive deficits
- Epilepsy
- Medical diagnosis or self-reported psychiatric illness
- Previous experience of using TENS
- Non-English speakers (unable to complete questionnaires)

---

### 9.3.3: Procedure:

---

The first testing session, lasting approximately 2 hours, is divided into six sections (Figure 9.3). The second testing session, lasting approximately 1 hour, follows the same procedure as the first session without steps 2 and 3 (Figure 9.4). Each step of the procedure will now be described in more detail.

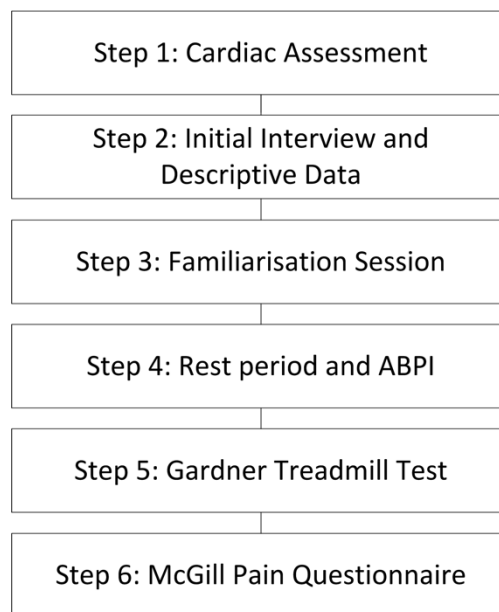


Figure 9.3: First testing session procedure

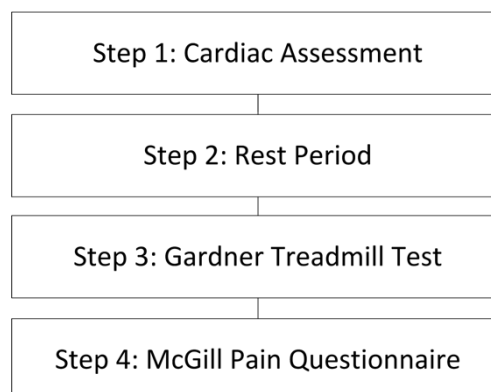


Figure 9.4: Second testing session procedure

#### 9.3.3.1: Cardiac Assessment:

---

Prior to the start of the testing session, a vascular medicine specialist undertook a cardiac assessment. The participant's heart was assessed by auscultation and if any abnormalities were evident, the participant was excluded from the study.

#### 9.3.3.2: Initial Interview and Descriptive Data:

---

An initial interview was conducted between the participant and the researcher. The study procedure was explained in detail and any questions addressed by the researcher.

Each participant completed four short questionnaires (Appendix 10):

1. Walking Impairment Questionnaire (Regensteiner et al 1990)
2. Pain Self-Efficacy Questionnaire (Nicholas 2007)
3. Pain Catastrophising Scale (Sullivan et al 1995)
4. Tampa scale of Kinesiophobia (Miller et al, 1991 (unpublished); Vlaeyen et al 1995)

These questionnaires aimed to provide data on walking impairment (1), and psychosocial factors including fear of pain (2), pain self-efficacy (3) and pain catastrophising (4). These questionnaires were chosen as they have all been shown to be valid and appropriate measures in a clinical population and they provide a good indication of the psychosocial aspects of PAD and IC.

#### 9.3.3.3: Familiarisation Session:

---

A familiarisation session was completed as per the Gardner Treadmill Protocol (Gardner et al 1991) (Appendix 11). The participant was connected to a 12-lead Echocardiograph (12-lead ECG) (GE CASE Premium Stress System), which recorded continuously throughout the procedure. The treadmill protocol was explained and the participant practiced walking on the treadmill at three different speeds (1mph, 1.5mph and 2mph) (GE CASE T-2100 Treadmill).

The self-report method of rating claudication symptoms was explained (1-5 scale where 1=None; 2=Onset; 3=Mild; 4=Moderate and 5=Severe, relating to symptoms of claudication). Further safety instructions were also issued: the participants were reminded to report any feelings of pain separate from claudication and any feelings of dizziness/light-headedness immediately so that the test can be stopped. This series of events took less than 10 minutes to complete and the participant walked for a maximum of 30 seconds at each treadmill speed.

#### 9.3.3.4: Rest Period and ABPI:

---

A rest period was then observed where the participant lay on a hospital bed in the testing room for 15 minutes. During this period, the participant's Ankle Brachial Pressure Index (ABPI) was measured using a handheld Doppler probe (Huntleigh Doppler D9000). Systolic blood pressures were measured in the right and left brachial, dorsalis pedis and posterior tibial arteries (McDermott et al 2006). The ABPI was calculated by dividing the mean of the dorsalis pedis and posterior tibial pressures in each leg by the mean of the brachial pressures. Five minutes prior to the end of the rest period the TENS machine was applied to the participant's calf and switched on.

#### 9.3.3.5: Gardner Treadmill Test:

---

The participant was helped onto the treadmill and the treadmill protocol commenced. This method requires the participant to walk at a normal pace on a treadmill. As the test proceeds, the gradient of the treadmill will increase by two degrees every two minutes. However, there is no increase in speed. The participant is asked to report when they reach their Initial Claudication Distance (ICD) i.e. when they first experience claudication symptoms. The participant then continues to walk until they report that they have reached their Absolute Claudication Distance (ACD) i.e. they cannot walk any further due to claudication symptoms. The treadmill is then stopped and the participant helped onto a bed where they lie down to rest (Gardner et al 1991).

Functional Claudication Distance (FCD) is another measure used with the Gardner Protocol (Kruidenier et al 2009b; Nicolai et al 2010). The principle is that patients with PAD and IC rarely walk to ACD daily. It has been found that they have a 'Functional Claudication Distance' (FCD), a level of pain at which they stop walking. This measure was explained to each participant and they were asked to indicate when they reached the point at which they would normally stop during the treadmill protocol. This allows the effects of the different types of TENS to be examined on a measure that is more relevant to the participant's daily function.

Once the participant reported ACD or 20 minutes of walking was completed, the treadmill was stopped, the participant is helped back to the bed and the TENS machine switched off.

#### Validity and Reliability:

---

The Gardner treadmill protocol is the most commonly used and validated method of inducing clinical ischaemic pain in patients with PAD (Kruidenier et al 2009b). Treadmill testing is the gold standard of measuring walking performance in patients with PAD (Coughlin et al 2006; Le Faucheur et al 2008).

In terms of reliability, test-retest intra-class reliability coefficients (ICC) between  $R = 0.89$  and  $0.95$  have been found for ACD (Gardner et al 1991; Nicolai et al 2009b). In a recent meta-analysis, Nicolai et al (2009b) examined the reliability of treadmill tests in patients with PAD. They compared studies that had investigated the reliability of either constant or graded (Gardner) treadmill protocols and used ICD and ACD as outcome measures. Eight studies were included of 658 patients. The ICC for ICD indicated that the two protocols were equally reliable although for ACD, the Gardner protocol is significantly more reliable with an ICC of  $0.95$  compared to that with constant protocol of between  $0.76$ - $0.91$  (Nicolai et al 2009b). There have been no further investigations of the reliability of the Gardner treadmill test published since this comprehensive meta-analysis.

#### 9.3.3.6: MPQ:

---

Pain quality was recorded using a retrospective MPQ (Melzack 1975) administered 5 minutes after the participant completed the treadmill protocol. The MPQ consists of a vocabulary of adjectives from which the participant chooses appropriate words to describe the particular qualities of IC pain sensation and accompanying feelings of distress and intrusion (Melzack 1975; Dworkin et al 2009).

#### 9.3.4: TENS Procedure:

---

The TENS machine was applied 5 minutes prior to each treadmill test and continued throughout the procedure. Each participant received one type of active TENS (HF-TENS or LF-TENS) during their first treadmill test. On the second treadmill test, all participants received P-TENS as a control.

A standard TENS machine was used (NeuroTrac 3 <sup>™</sup>, Verity Medical Ltd, Surrey, UK). Placement sites were determined from the report of the participants, relating to where they usually experience IC pain when walking. These sites were prepared using an Alcowipe (Universal Hospital Supplies Ltd, UK) and standard sharp/blunt skin sensation testing was completed over the area using single use sterile Neurotips (Owen Mumford Ltd, Woodstock, Oxford, UK). A segmental electrode application was employed using self-adhesive carbon rubber electrodes measuring 5x5 cm (PhysioMed PALS<sup>®</sup> electrodes, Glossop, UK). The placement sites were commonly over the gastrocnemius muscle belly, at least 2cm apart. The superior electrode was positioned so that it covered the superior edge of the pain described and the inferior electrode similarly so that it covered the inferior edge of the area of pain. The electrodes were attached to the TENS unit via the dedicated manufacturer leads.

The TENS machine was a portable dual channel device with an asymmetrical biphasic waveform, which was calibrated prior to use using a digital oscilloscope and tested manually by the examiner prior to every testing session. The stimulation parameters were selected based on those commonly used in clinical practice and identified as efficacious in the TENS



literature (Chen et al 2008). The TENS unit was calibrated to 120Hz, 200 $\mu$ s and patient determined intensity of “strong but comfortable” for the HF-TENS stimulation. For LF-TENS, the unit was calibrated to 2Hz, 200 $\mu$ s and patient determined intensity of “strong but comfortable and slight muscle twitch”.

The Placebo stimulation was achieved using the same TENS unit and programmed settings. However, a different lead was used with a break in the wires, covered by electrical tape with the aim of making it inconspicuous (Figure 7.13). This allowed the unit to be switched on and appear as if current was being applied. This was checked and confirmed with the use of an oscilloscope as above. For the purpose of blinding, the participants were told that different ‘dosages’ of TENS were being tested and that some of these dosages, stimulation might not be perceivable.

---

#### 9.3.5: Statistical Analysis:

---

Figure 9.5 summarises the analysis procedures followed. The mean scores for ICD, FCD and ACD were positively skewed (0.930 to 1.615) and showed heteroscedascity ( $p < 0.05$  Levene’s test i.e. increasing variance in SD). Therefore, a log (10) transformation was applied to normalise the data. However, transformation did not address the variance within the data and thus non-parametric statistics were used to analyse the data.

Wilcoxon Signed Ranks tests were used to examine for within group differences in treadmill measures. Individual changes in ICD, FCD and ACD between P-TENS and Active TENS were calculated for each participant. Distance walked with P-TENS was subtracted from that with Active TENS. The median was then calculated for each group and used for analysis using Mann-Whitney U tests. Individual percentage change was also calculated for ICD, FCD and ACD. The difference between the two sessions was calculated as a percentage of the distance walked with P-TENS. These percentages were employed as a method to examine the effect of TENS on walking distance, regardless of baseline ability. For each group, the median percentage change was calculated. These values were used for analysis and differences between groups examined with Mann-Whitney U tests. Wilcoxon signed ranks

tests were also used to examine for differences in PRI score within the groups and Mann-Whitney U tests were employed to examine for any changes between groups.

The data were then pooled in an effort to examine the overall effects of the application of TENS. Data for all participants with Placebo TENS was compared to those with Active TENS using Wilcoxon Signed Ranks tests.

Interrelationships between measures were analysed using bivariate Spearman's correlation coefficients. Treadmill measures with placebo TENS were taken as 'baseline' data and analysed for any relationships with demographic variables. The same analysis was used to examine the relationships between measures with TENS intervention, termed 'experimental' measures.

Multiple linear regression analyses were used to investigate the predictors of 1) Baseline ACD and 2) Change in ACD ( $\Delta$ ACD). Similar to the method employed by Kruidenier et al (2009a) the simultaneous ('enter') method was used to add all pre-selected variables into the regression analysis in one step. A maximum of eight predictor variables was set to reduce the possibility of Type I or II errors (Topliss and Costello 1972; Todeschini et al 2004). Included in the models were the factors reported in published literature as the best predictors of walking distance in patients with PAD and IC (ABPI, BMI and WIQ) (McDermott et al 1999; Kruidenier et al 2009a). Added to the models were any additional variables found to correlate most closely with ACD and  $\Delta$ ACD in the current study (PSEQ and Change in TENS intensity ( $\Delta$ mA) respectively).

Statistical significance was set at  $p = 0.05$  (two-tailed) and analysis was performed using SPSS version 19.0.

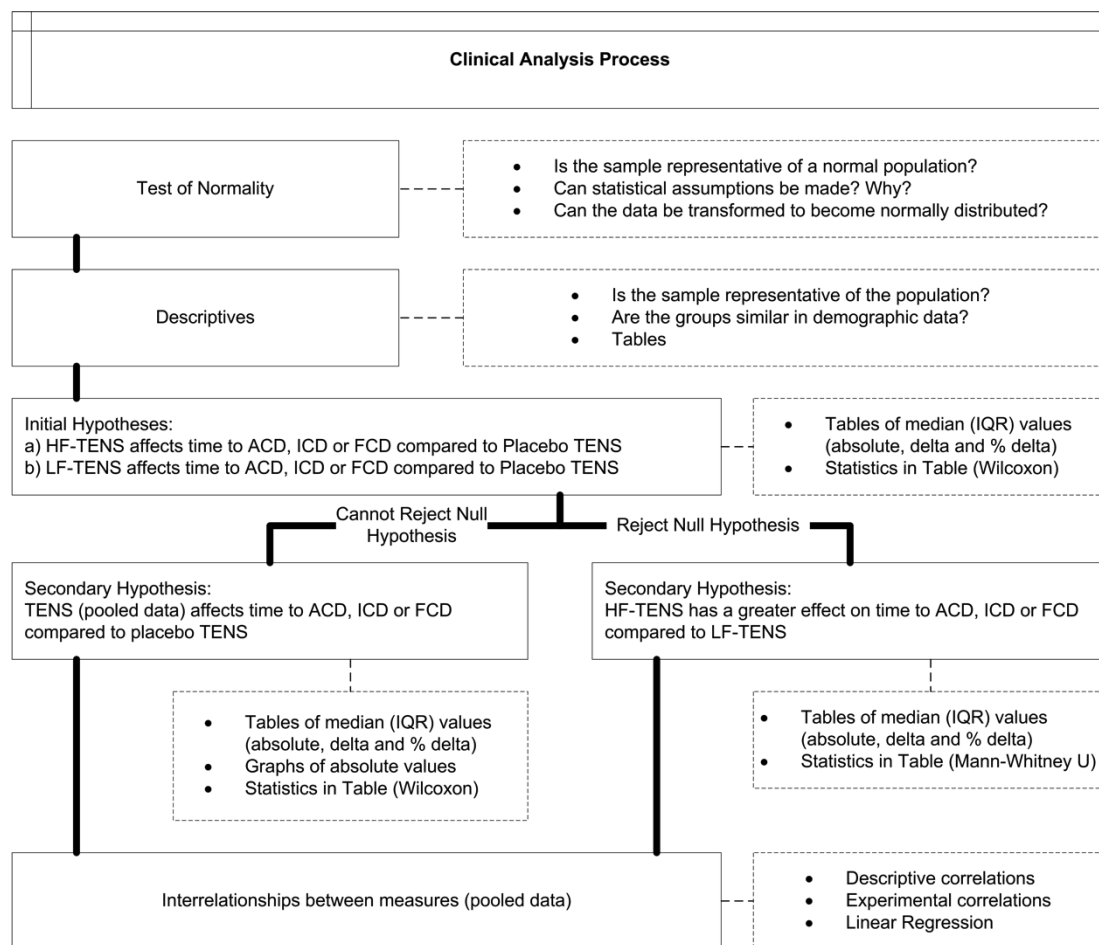


Figure 9.5: Summary of data analysis plan

## 9.4: RESULTS:

### 9.4.1: Participants:

The participants were 40 patients with PAD and IC without previous experience of TENS or other exercise limiting pathologies. They were recruited by the principal researcher via oral explanation of the study at the claudication clinic. Four participants were excluded from analysis due to non-completion of the experimental procedure. Three had exercise-limiting co-morbidities and one was unable to walk safely on the treadmill. Thirty-six participants were included in the analysis (29 male, mean age 70 years, range = 54-87 years). Figure 9.6 summarises this information and displays the progress of participants through the study.

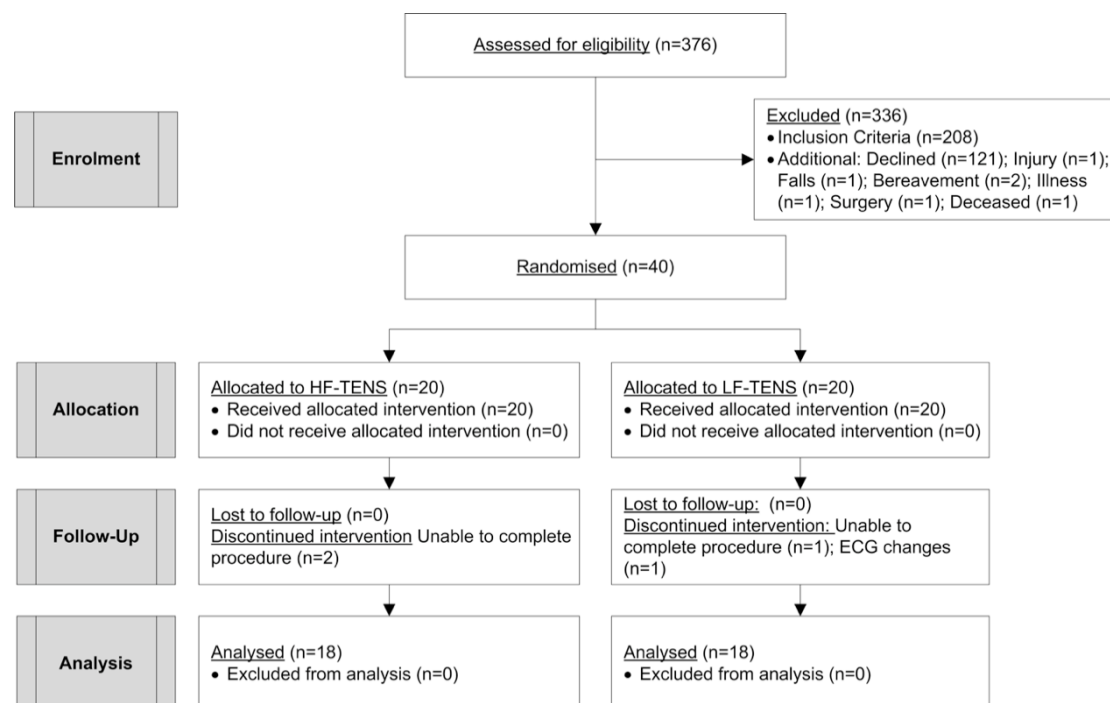


Figure 9.6: CONSORT diagram displaying the progression of participants through the study.

Demographic data for the participants are detailed in Table 9.1. The high BP and ABPI recordings were due to diabetes-related incompressible vessels and inaccurate blood pressure readings. The disease-specific functional measure (WIQ) is representative of PAD patients with Fontaine Stage II Claudication (Nicola et al 2009a). The scores recorded with the psychosocial measures (PSEQ, PCS and TSK) were similar to those reported in patients

with chronic pain conditions (van Damme et al 2002; Nicholas et al 2008; Roelofs et al 2011).

Table 9.1: Demographic and baseline data for all participants included in the study. The *p* values stated relate to independent student's *t*-tests (two tailed) of the group values.

	All				HF-TENS Group		LF-TENS Group		<i>p value</i>
	Mean	SD	Min	Max	Mean	SE	Mean	SE	
<b>Age (years)</b>	70	8.0	54	87	68	1.8	71	1.9	0.344
<b>BMI (kg/m<sup>2</sup>)</b>	28	4.2	22	39	29	1.0	27	1.0	0.261
<b>HR (bpm)</b>	71	9.4	53	94	71	2.0	71	2.4	0.986
<b>BP (mmHg)</b>	146	18.1	110	202	147	5.2	146	3.2	0.943
<b>ABPI (AU)</b>	.63	.164	.24	.99	.70	.041	.57	.031	0.020*
<b>WIIQ (%)</b>	48	19.5	6	91	50	4.9	45	4.3	0.482
<b>PSEQ (0-60)</b>	40	12.5	10	60	40	2.7	41	3.2	0.714
<b>PCS (0-52)</b>	12	12.1	0	40	13	3.0	11	2.7	0.588
<b>TSK (17-68)</b>	38	7.9	25	54	39	1.6	37	2.1	0.418
<b>ICD (m)</b>	86	51.7	22	271	85	15.5	88	8.1	0.867
<b>FCD (m)</b>	202	127.1	70	545	222	32.4	182	27.4	0.351
<b>ACD (m)</b>	259	169.2	99	806	268	39.4	250	41.4	0.750
<b>PRI (0-78)</b>	21	7.9	2	38	20	1.9	23	1.8	0.219

**Table 9.1 Key:**

BMI = Body Mass Index

HR = Heart Rate

BP = Systolic Blood Pressure

ABPI = Ankle Brachial pressure Index (measured in arbitrary units (AU))

WIIQ (%) = Walking Impairment Questionnaire

PSEQ (0-60) = Pain Self Efficacy Scale

PCS (0-52) = Pain Catastrophising Scale

TSK (17-68) = Tampa Scale of Kinesiophobia

ICD = Initial Claudication Distance

FCD = Functional Claudication Distance

ACD = Absolute Claudication Distance

PRI (0-78) = Pain Rating Index

Table 9.1 details the demographic data for the participants in each group. The groups are similar in terms of demographic and disease data except for ABPI. The LF-TENS group had a significantly lower mean ABPI ( $t(34) = 2.442$ ) (Table 9.1).

#### 9.4.2: Within Group Profiles (HF-TENS and LF-TENS vs. P-TENS):

Treadmill data were not normally distributed therefore non-parametric tests were used for analysis. Data are presented as median and inter quartile range (IQR).

ICD, FCD and ACD (metres) with placebo and with active TENS for each group are detailed in Table 9.2 and in Figure 9.7. Median walking distance increased with TENS intervention in both groups, except FCD with HF-TENS and ICD with LF-TENS. Wilcoxon Signed Ranks tests of treadmill measures showed significant differences in all measures between placebo and HF-TENS (Table 9.2). For LF-TENS, the difference was significant only at ACD ( $Mdn = 228$  and  $179$ ,  $W_s = 39$ ,  $z = 2.025$ ,  $p = 0.043$ ,  $r = 0.48$ ). There was no change in PRI scores for either group (Table 2).

Table 9.2: Median (IQR) ICD, FCD and ACD (in metres) and PRI scores for both groups with placebo and with TENS intervention. \* = significant change within group.

		Placebo	Intervention	<i>p</i>	<i>W<sub>s</sub></i>	<i>r</i>
<b>HF-TENS Group</b>	<b>ICD</b>	61 (68)	82 (112)	.004*	18	.69
	<b>FCD</b>	187 (175)	175 (303)	.025*	34	.53
	<b>ACD</b>	211 (244)	212 (297)	.025*	34	.53
	<b>PRI</b>	19 (8.5)	24 (13.3)	.476	48	.17
<b>LF-TENS Group</b>	<b>ICD</b>	81 (38)	76 (50)	.965	85	.01
	<b>FCD</b>	151 (130)	158 (114)	.687	62	.16
	<b>ACD</b>	179 (153)	228 (218)	.043*	39	.48
	<b>PRI</b>	24 (11.5)	21 (17)	.601	74	.12

#### 9.4.3: Between Group Profiles (HF-TENS vs. LF-TENS):

Table 9.3 details the median change and median percentage change in the measures for both groups. There was an increase in all measures from baseline in both groups. Mann-Whitney U tests showed significant differences between the groups only for change, and percentage change in ICD ( $Mdn = 26$  with HF-TENS and  $6$  with LF-TENS,  $U = 268$ ,  $z = 2.073$ ,  $p = 0.038$ ,  $r = 0.49$  and  $Mdn = 43$  with HF-TENS and  $9$  with LF-TENS,  $U = 267$ ,  $z = 2.088$ ,  $p =$

0.037,  $r = 0.49$  respectively). Figures 9.8 and 9.9 illustrate these findings, showing the increases in FCD and ACD in both groups and the greater increase in ICD in the HF-TENS group.

Table 9.3: Median (IQR) change and percentage change in ICD, FCD, ACD and PRI scores for HF and LF-TENS groups. \* = significant change between groups.

		<b>HF-TENS Group</b>	<b>LF-TENS Group</b>	<b><i>p</i></b>	<b><i>U</i></b>	<b><i>r</i></b>
<b>Change</b>	<b>ICD</b>	26 (71)	6 (67)	.038*	268	.49
	<b>FCD</b>	26 (70)	4 (55)	.268	298	.26
	<b>ACD</b>	30 (76)	23 (93)	.887	329	.03
	<b>PRI</b>	0.5 (6.3)	1.5 (11.3)	.949	331	.01
<b>% Change</b>	<b>ICD</b>	43 (64)	9 (79)	.037*	267	.49
	<b>FCD</b>	9 (38)	3 (32)	.393	306	.20
	<b>ACD</b>	13 (30)	18 (43)	.752	323	.07
	<b>PRI</b>	2 (38)	7 (50)	.975	332	.01

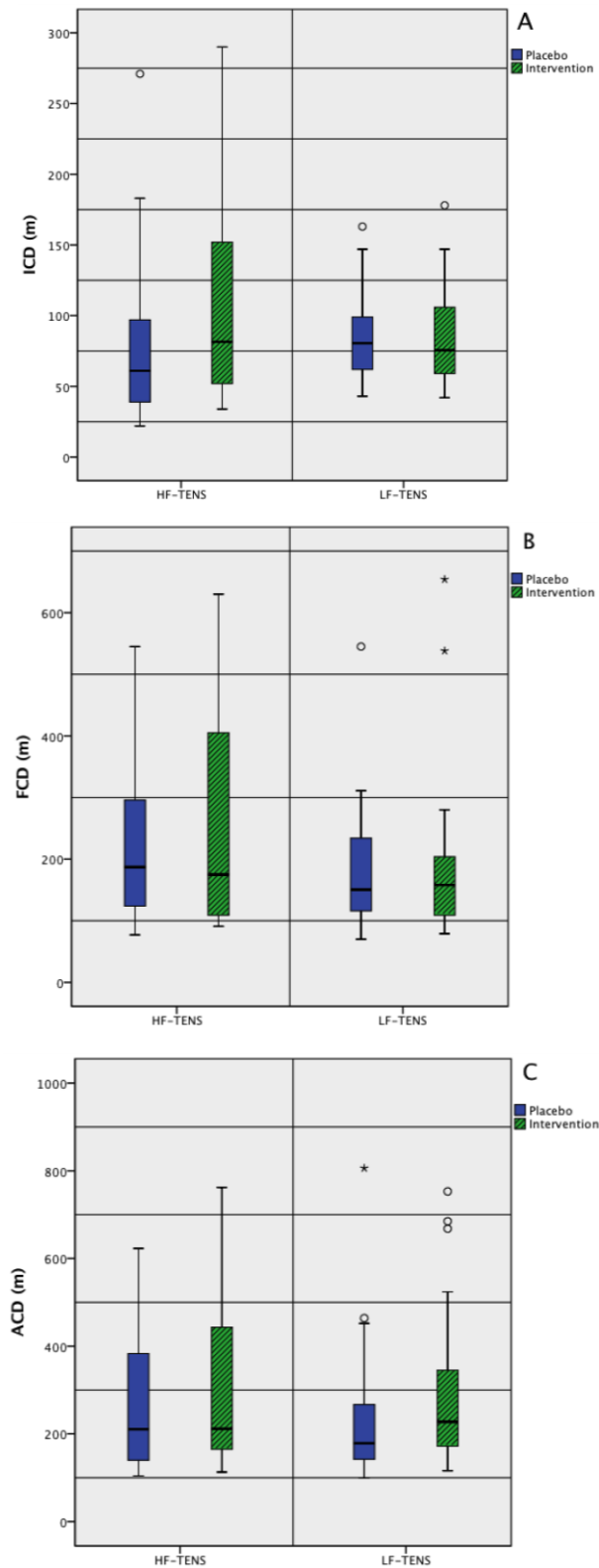


Figure 9.7: Graphs of A) ICD, B) FCD and C) ACD with placebo and intervention for both groups. Significant differences were found for ICD, FCD and ACD with HF-TENS ( $p = .004$ ,  $.025$  and  $.025$  respectively). For LF-TENS, only difference observed was in ACD ( $p = .043$ ).



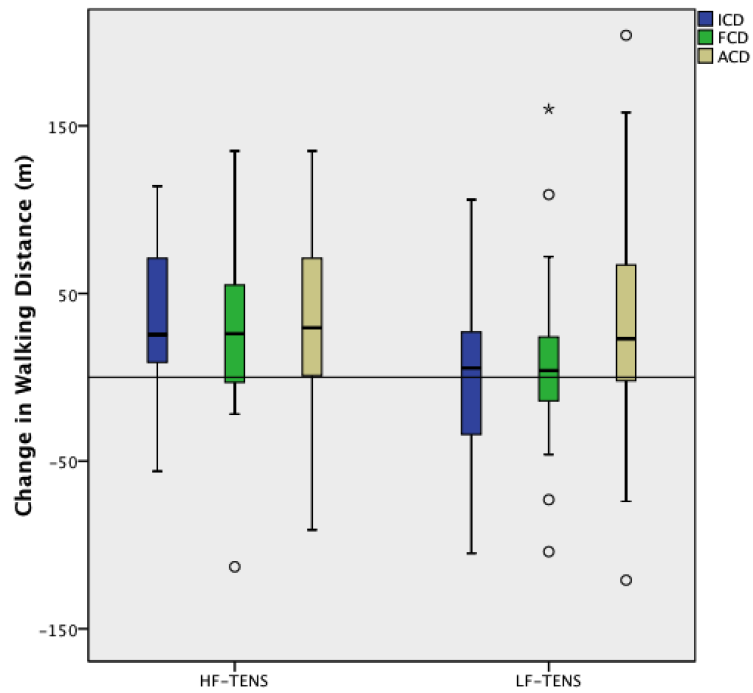


Figure 9.8: Boxplots representing change in walking measures with intervention in both groups. Error bars = IQR. The only significant difference between the groups was for change in ICD.

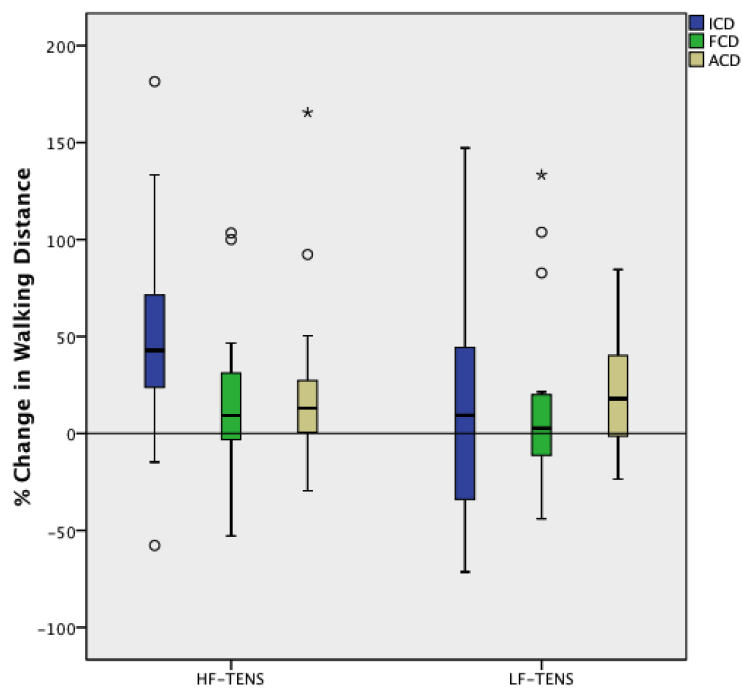


Figure 9.9: Boxplots representing percentage change in walking measures with intervention in both groups. Error bars = IQR. The only significant difference between the groups was for percentage change in ICD.

#### 9.4.4: Pooled treadmill analysis:

With the aim of analysing the overall effects of TENS on walking performance, the treadmill walking measures were pooled between the groups. This resulted in overall median ICD, FCD and ACD distances for all participants with Placebo and with Active TENS (Figure 9.10). When these data were analysed, ICD, FCD and ACD were found to increase with Active TENS. The greatest effect of TENS was observed for ACD: 176m to 211.5m with a moderate effect size of 0.49 (Figure 9.10). Despite the pooling of the data, variance in the sample was still significant (see the error bars in Figure 9.10).

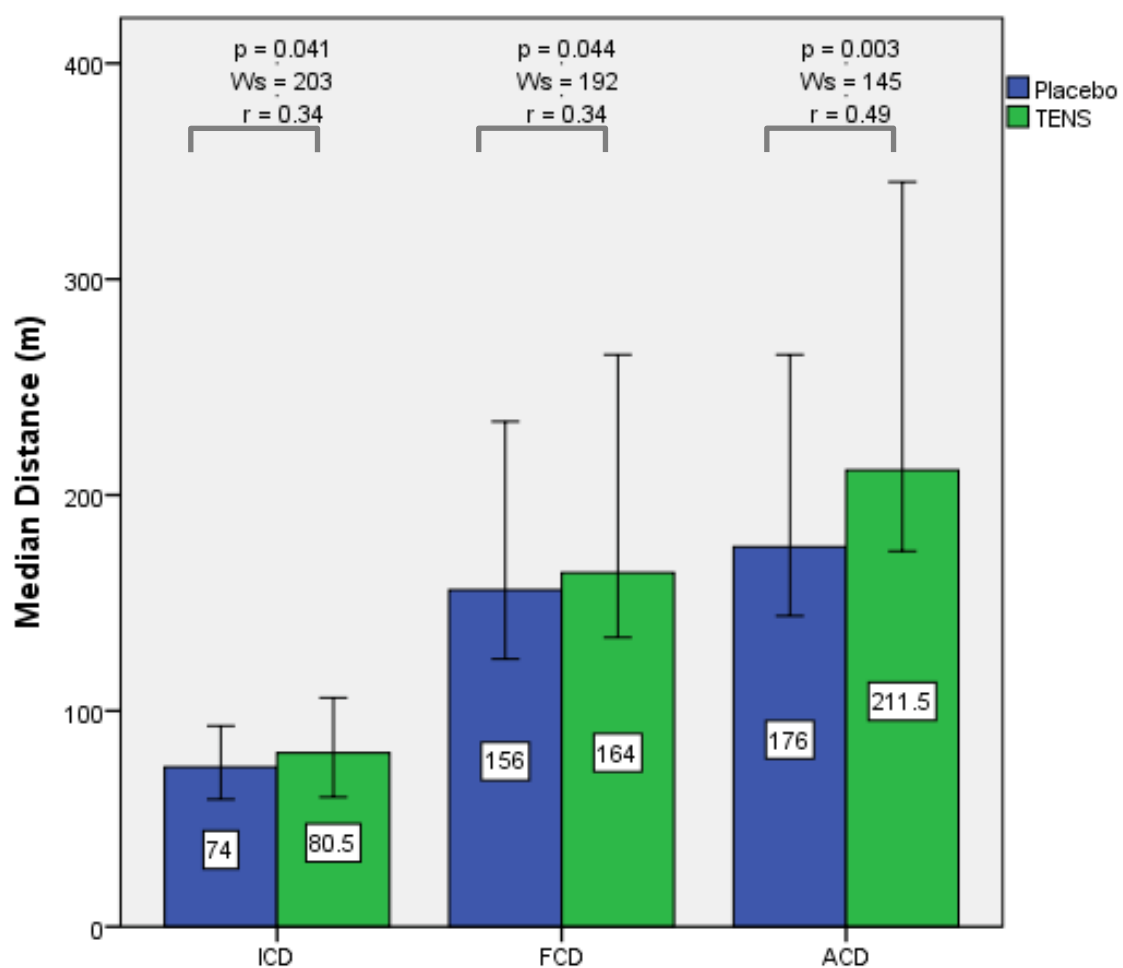


Figure 9.10: Median ICD, FCD and ACD for all participants with Placebo and Active TENS. Statistics: Wilcoxon Signed Ranks tests. Error bars = 95% CI.

---

#### 9.4.5: Interrelationships between variables:

---

##### 9.4.5.1: Descriptive and Baseline Measures:

---

Correlations between the baseline measures in all participants are detailed in Table 9.4. Significant relationships were observed between Age and BMI ( $r_s = 0.52, p = 0.001$ ), BMI and PSEQ score ( $r_s = 0.39, p = 0.019$ ) and HR and PCS score ( $r_s = 0.36, p = 0.030$ ).

Scores on the WIQ were related to those on the PSEQ and PCS ( $r_s = 0.66, p < 0.001$  and  $r_s = -0.37, p = 0.025$  respectively) along with FCD and ACD ( $r_s = 0.56, p < 0.001$  and  $r_s = 0.46, p = 0.005$  respectively). PSEQ responses showed the largest number of correlations with significant relationships found with PCS ( $r_s = -.62, p < 0.001$ ), TSK ( $r_s = -.62, p < 0.001$ ), FCD and ACD ( $r_s = 0.44, p = 0.007$  and  $r_s = 0.37, p = 0.026$  respectively) and also with PRI of the MPQ ( $r_s = -.34, p = 0.042$ ).

PCS scores were related to those on the TSK ( $r_s = 0.57, p < 0.001$ ). Treadmill measures were highly correlated with each other but not with the measures of disease (ABPI) or pain (PRI) (Table 9.4). Heart rate at ICD and ACD was negatively related to BMI ( $r_s = 0.42, p = 0.016$  and  $r_s = 0.44, p = 0.011$  respectively). Heart rate at ACD was also related to WIQ score ( $r_s = 0.36, p = 0.39$ ) (Table 9.4).

##### 9.4.5.2: Experimental Measures:

---

Correlations between the experimental measures are detailed in Table 9.5. Significant relationships were found between BMI and Change in ICD ( $\Delta$ ICD) ( $r_s = 0.34, p = 0.040$ ) along with change in TENS Intensity and change in ACD ( $r_2 = 0.35, p = 0.040$ ). Change in ICD and FCD was related to Heart Rate at ICD ( $r_s = 0.47, p = 0.005$  and  $r_s = 0.47, p = 0.006$  respectively) and Heart Rate at ACD ( $r_s = 0.54, p = 0.001$  and  $r_s = 0.44, p = 0.011$  respectively).

Table 9.4: Spearman's Correlation Coefficients between baseline measures in all participants

	Age	BMI	BP (sys)	HR	ABPI	WIQ	PSEQ	PCS	TSK	ICD	FCD	ACD	HR ICD	HR ACD
<b>BMI</b>	<b>-.522**</b>													
<b>BP (sys)</b>	.245	-.032												
<b>HR</b>	-.099	-.197	-.138											
<b>ABPI</b>	-.262	.296	-.037	-.177										
<b>WIQ</b>	.054	-.177	.068	-.136	.060									
<b>PSEQ</b>	.253	<b>-.388*</b>	.314	-.261	-.073	<b>.657**</b>								
<b>PCS</b>	-.087	.198	-.230	<b>.362*</b>	-.110	<b>-.373*</b>	<b>-.621**</b>							
<b>TSK</b>	-.041	.299	-.329	.177	.003	-.288	<b>-.621**</b>	<b>.565**</b>						
<b>ICD</b>	.169	-.200	.113	-.019	-.139	.253	.325	-.066	.004					
<b>FCD</b>	.057	-.115	.121	-.058	.058	<b>.555**</b>	<b>.439**</b>	-.086	-.195	<b>.775**</b>				
<b>ACD</b>	.031	-.148	.056	-.045	-.017	<b>.458**</b>	<b>.371*</b>	-.116	-.140	<b>.788**</b>	<b>.905**</b>			
<b>HR ICD</b>	.165	<b>-.417*</b>	.318	.287	-.078	.259	.245	-.089	-.098	.320	.269	.099		
<b>HR ACD</b>	.090	<b>-.438*</b>	.277	.293	.027	<b>.360*</b>	.314	-.149	-.187	.288	.336	.161	<b>.933**</b>	
<b>PRI</b>	-.200	.079	-.165	.286	-.136	-.243	<b>-.340*</b>	.294	.144	-.234	-.227	-.134	-.170	-.232

\* Correlation is significant:  $p < 0.05$  (2-tailed). \*\* Correlation is significant:  $p < 0.01$  (2-tailed).

Table 9.5: Spearman's Correlation Coefficients between descriptive and experimental measures

	Age	BMI	BP (sys)	HR	ABPI	$\Delta$ mA	WIQ	PSEQ	PCS	TSK	$\Delta$ ICD	$\Delta$ FCD	$\Delta$ ACD	$\Delta$ PRI	HR ICD
<b><math>\Delta</math>ICD</b>	-.116	<b>.344*</b>	-.185	-.003	.067	.004	-.008	-.218	.328	.260					
<b><math>\Delta</math>FCD</b>	.030	-.118	-.191	.051	.058	.218	-.073	-.079	.076	.043	<b>.519**</b>				
<b><math>\Delta</math>ACD</b>	.088	-.055	-.075	-.246	.163	<b>.350*</b>	-.100	-.072	-.082	.057	.262	<b>.506**</b>			
<b><math>\Delta</math>PRI</b>	-.147	.322	.061	.034	-.207	-.082	.212	-.049	.061	.201	.015	-.160	-.091		
<b>HR ICD</b>	.165	<b>-.417*</b>	.318	.287	-.078	.168	.259	.245	-.089	-.098	<b>-.474**</b>	<b>-.469**</b>	-.306	-.008	
<b>HR ACD</b>	.090	<b>-.438*</b>	.277	.293	.027	.260	<b>.360*</b>	.314	-.149	-.187	<b>-.536**</b>	<b>-.437*</b>	-.340	.016	<b>.933**</b>

\* Correlation is significant:  $p < 0.05$  (2-tailed). \*\* Correlation is significant:  $p < 0.01$  (2-tailed).

Table 9.5 Key:

$\Delta$ mA = change in TENS intensity;

$\Delta$ ICD = change in ICD;

$\Delta$ FCD = change in FCD;

$\Delta$ ACD = change in ACD;

$\Delta$ PRI = change in PRI score.

HR ICD = Heart Rate at ICD

HR ACD = Heart Rate at ACD

---

#### 9.4.6: Predictors of ACD and Change in ACD:

---

##### 9.4.6.1: ACD

---

Enter regression analysis was performed for ACD with placebo using four predictor variables: ABPI, BMI, WIQ and PSEQ. A significant model emerged ( $F_{4,31} = 3.050$ ,  $p = 0.31$ ), adjusted  $R^2 = 0.19$ . Variables entered into the model are shown in Table 9.6. Collinearity diagnostics indicated that any relationships between the predictor variables did not affect the regression model (shown by tolerance values greater than 0.10 Table 9.6).

Table 9.6: Multiple regression analysis for ACD.

Predictor Variable	Standardised Beta	<i>p</i>	Tolerance
ABPI	-.008	.960	0.888
BMI	-.052	.764	0.788
WIQ	.326	.108	0.594
PSEQ	.241	.247	0.555

##### 9.4.6.2: Change in ACD

---

Enter regression analysis was performed for  $\Delta$ ACD using five predictor variables: ABPI, BMI, WIQ, PSEQ and  $\Delta$ mA. A significant model emerged ( $F_{5,30} = 4.829$ ,  $p = 0.002$ ), adjusted  $R^2 = 0.35$ . Variables entered into the model are shown in Table 9.7. Only  $\Delta$ mA was found to be a significant predictor of  $\Delta$ ACD. Collinearity diagnostics indicated that any relationships between the predictor variables did not affect the regression model (shown by tolerance values greater than 0.10 Table 9.7).

Table 9.7: Multiple regression analysis for  $\Delta$ ACD.

Predictor Variable	Standardised Beta	<i>p</i>	Tolerance
ABPI	.108	.474	0.837
BMI	-.129	.412	0.771
WIQ	-.220	.222	0.594
PSEQ	-.080	.667	0.540
$\Delta$ mA	.633	.000	0.869

---

#### 9.4.7: Summary of Analysis and Results:

---

Figure 9.11 details the analyses completed and the main outcomes.

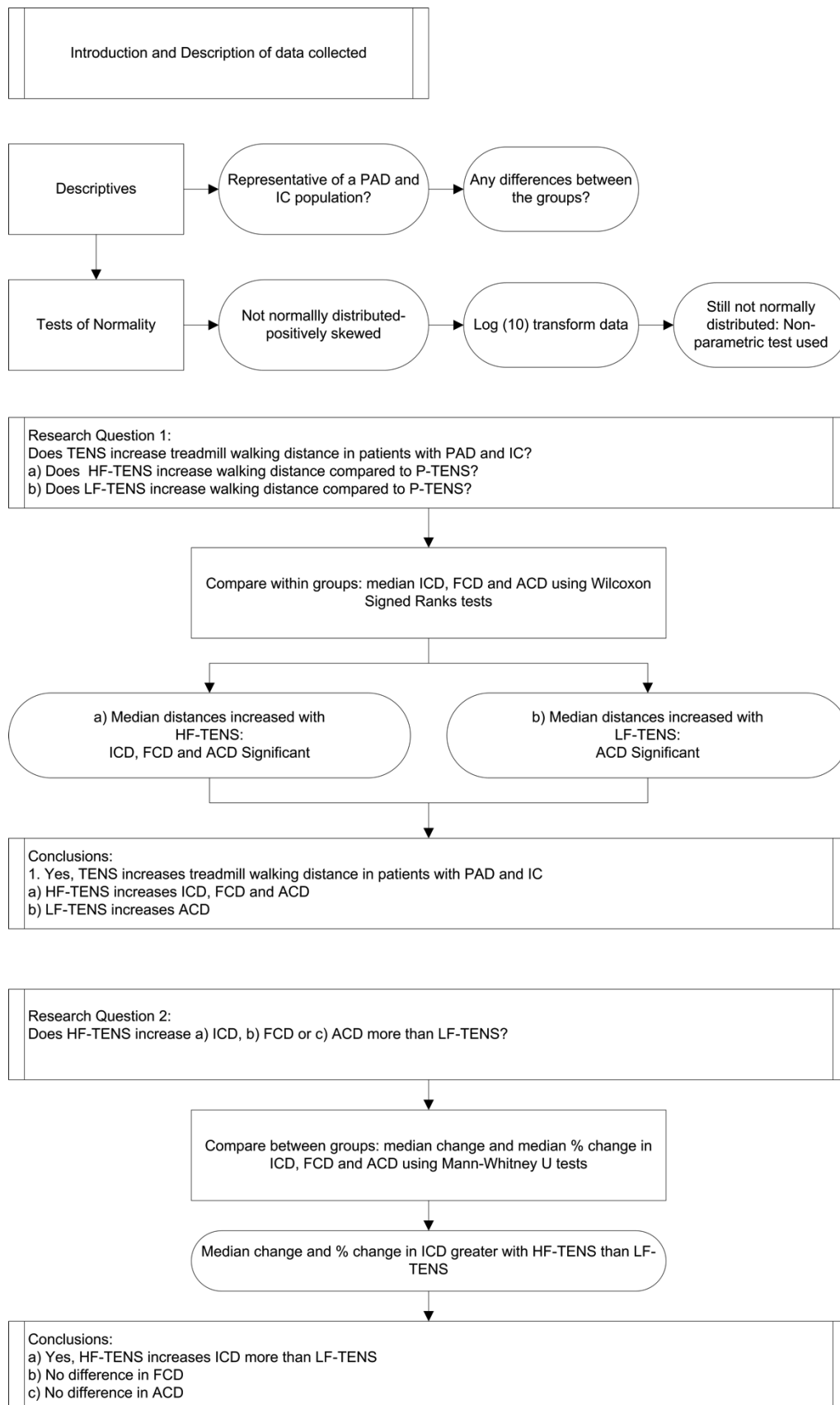


Figure 9.11: Summary of analysis and main outcomes

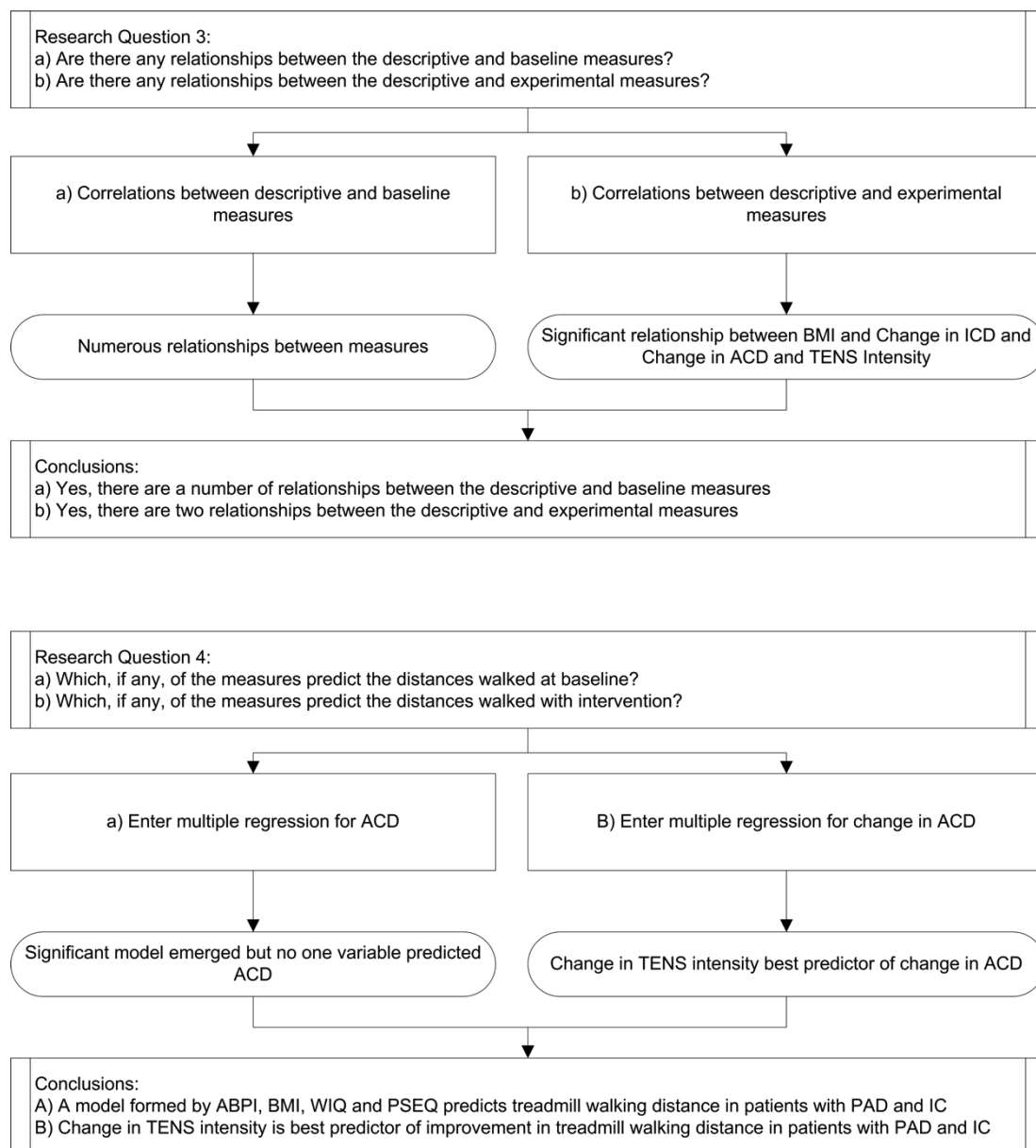


Figure 9.11 (continued): Summary of analysis and main outcomes



## 9.5: DISCUSSION:

---

The study discussed is a 'proof of concept' study and the results must be interpreted as such. Nevertheless, the results of this study show that compared to placebo, TENS increases walking performance in patients with IC. These results indicate that TENS is an effective intervention that allows patients with IC to walk further before onset, and while experiencing pain.

The different types of TENS employed in this study were found to affect distinctive aspects of the pain experience. ICD, FCD and ACD increased with HF-TENS whereas only ACD increased with LF-TENS. This indicates different mechanisms of hypoalgesia and possibly distinct neurophysiological effects of the different frequencies of TENS. Conclusions regarding the potential of either of these types of TENS to be more effective than the other for this patient population are outwith the scope of this study.

The only predictor of change in walking performance with intervention was patient-controlled intensity of TENS. This finding indicates that the changes in walking performance observed were related to the application of TENS and more specifically, the decisions of the patient to increase the intensity of TENS stimulation to overcome the pain experienced.

The contribution of this study to the issues of improving walking performance in patients with PAD and IC is novel. No other study in the published literature has examined the effects of using TENS while exercising on walking performance in this patient population.

An evaluation of these findings will be presented and discussed below in relation to the context of this thesis, other findings in the published literature and possible future directions for research.

---

### 9.5.1: TENS and increased walking performance:

---

The original research question was: ‘what are the effects of TENS on walking performance in patients with IC?’ The results of the current study suggest that compared to placebo TENS, HF-TENS and LF-TENS increase treadmill walking performance in patients with PAD and IC.

As discussed in Chapter 8, HF-TENS is proposed to act by activating large diameter mechanoreceptors ( $A\beta$ -fibres), delta ( $\delta$ )-opioid receptors and increasing gamma-Aminobutyric acid (GABA) in the spinal cord and is associated with immediate, localised, segmental inhibition as conceived by the original gate control theory (Melzack and Wall 1965; Andersson 1979; Sluka and Walsh 2003; DeSantana et al 2008; Chen and Johnson 2011). LF-TENS was originally theorised to act on smaller diameter nociceptive afferents, brainstem structures and supraspinal descending pathways, releasing endogenous opiates centrally and peripherally (Sjolund et al 1977; DeSantana et al 2008). It was thought that LF-TENS did not induce hypoalgesia immediately but takes a few minutes to provide effective pain relief due to its more complex mechanisms (Le Bars 2002). However, more recent research has cast doubt on this distinction between the mechanisms of action of these two types of TENS (Radhakrishnan and Sluka 2005). Nevertheless, the originally proposed mechanisms of action and characteristics of hypoalgesia seem to be evident in the current study.

Figures 9.8 and 9.9 shows the change in treadmill walking distances in both groups with scores above zero representing an increase in walking distance with TENS intervention. Increases in ICD, FCD and ACD were observed in the HF-TENS group suggesting an immediate and prolonged hypoalgesic effect. The increases in median ICD and ACD with HF-TENS were found to be significant with effect sizes of 0.69 ( $p = 0.004$ ) and 0.53 ( $p = 0.025$ ) respectively (Table 9.2). In the LF-TENS group, there was a decrease in median ICD but increases in FCD and ACD suggesting a delayed but effective hypoalgesic effect at tolerance. The increase in ACD with LF-TENS was found to be significant with an effect size of 0.48 ( $p = 0.043$ ) (Table 9.2). These findings suggest that HF-TENS had an immediate and lasting effect, reducing pain at the mild (ICD) and more severe parts of the pain experience (FCD and ACD).

With LF-TENS however, hypoalgesic effects are evident only when the pain was severe (ACD) indicating a delayed action. Therefore the results from this study appear to support the proposed segmental, spinal mechanisms of HF-TENS and supraspinal, delay-action opiate mechanism of LF-TENS.

The effects of HF, and LF-TENS stimulation have been examined extensively within the published literature. Due to the complex nature of clinical pain and the limited ability to control stimulation and experience, investigations have been conducted on experimental pain. Mixed effects have been reported from studies employing a multitude of different stimulation parameters (Chen et al 2008; Claydon et al 2011). Due to this variation, definitive evidence of dose-related effects of TENS frequency is limited (Chen et al 2008; Claydon et al 2011). Parameter combinations have been found to elicit different effects depending on pain model investigated (Claydon et al 2011).

Experimental ischaemic pain provides an ideal method of examining the differential effects of TENS parameters on the pain experience. Induction of ischaemic pain allows investigation of pain through the full time course: from pain threshold to tolerance and during the steady development of intensity throughout (Woolf 1979). Of the studies that have investigated the effects of TENS frequency on induced ischaemic pain, mixed results are reported (Roche et al 1984; Walsh et al 1995a; Foster et al 1996; Chen and Johnson 2011). In the most recent high quality study, not included in the reviews by Chen et al (2008) or Claydon et al (2011), the effects of HF-TENS was compared to LF-TENS in a model of upper limb ischaemic pain (Chen and Johnson 2011). Unfortunately, due to the use of a modified method of pain induction and repeated measures design, time to pain threshold and tolerance was not recorded. The authors reported that compared to P-TENS, a decrease in pain intensity was observed with HF-TENS at 1 and 2 minutes however, with LF-TENS, an increase in pain intensity was observed at the same time points (Chen and Johnson 2011). These findings suggest that HF-TENS is more effective in reducing pain intensity at the initial stages of the pain experience (all mean VAS scores were less than 50mm, or 5 out of 10 i.e. mild to moderate levels of pain (Buer and Linton 2002)). These findings are similar to those in the

current study of clinical ischaemic pain. At the pain threshold level of the pain experience, the time to perception of pain was prolonged with HF-TENS whereas with LF-TENS the median time to pain threshold (ICD) actually decreased, suggesting an increase in pain intensity (Table 9.2 and Figure 9.7a).

The different effects observed with HF and LF-TENS are hypothesised to be a result of a more effective electrical paraesthesia induced with greater frequencies stimulating ectopic impulses and producing abnormal patterns of neural activity (Kiernan et al 1997; Mogyoros et al 2000). As LF-TENS produces little or no paraesthesia, the initial experience of pain would be unaffected. When the pain experience develops to become more intense, LF-TENS stimulation of  $\mu$ -opioid receptors and release of serotonin and action at 5HT<sub>2</sub> and 5HT<sub>3</sub> receptors becomes effective and a reduction in pain is observed at near-tolerance levels. In the study by Chen and Johnson (2011), mean pain intensity score with LF-TENS at minute 2 was lower than at minute 1 possibly indicating the beginnings of a hypoalgesic effect although this reduction was also observed with no-TENS and P-TENS to a similar extent. This general reduction in pain, regardless of the intervention may indicate the endogenous opioid response to the induction of pain, thus somewhat masking the effect of LF-TENS.

Compared to P-TENS, median change in ACD with HF-TENS was 30 metres (m) and with LF-TENS, 23m. This relates to percentage increases of 13% for HF-TENS and 18% with LF-TENS (Table 9.3 and Figure 9.9). As mentioned at the beginning of this chapter, a 60% improvement in ACD has been suggested as a worthwhile improvement in walking distance for patient with IC (Oakley et al 2008). The effect of TENS on IC pain does not achieve this level of improvement although the current study was designed in such a manner that would lead to underestimation of the effect of TENS. As a familiarisation or training effect has been shown with the Gardner treadmill test (Labs et al 1999), P-TENS condition was examined on the second testing session for every participant so that any effect of TENS could not be confused with general improvement in completing the testing procedure. By the nature of this design, any effect of TENS observed would be underestimated. The training effect for the Gardner treadmill protocol has been found to be 10% for ACD (Labs et al 1999). With

this in mind, the significant increases of 13 and 18% with HF and LF-TENS may move closer to the proposed clinically worthwhile improvement. When compared to placebo, improvements in ACD of approximately 30% have been found with IC medication (Momsen et al 2009). The change in ACD with TENS intervention, taking into account the possible treadmill training effect (10%) is close to this level of improvement (increase of 23% and 28% compared to placebo).

TENS has been shown to elicit a strong placebo response (Roche et al 1984; Marchand et al 1993; Roche et al 2002). A placebo response is an important finding, especially in patients with chronic pain. Reduction in reported pain with placebo analgesia is achieved through complex and integrated psychological and physical mechanisms including 'expectations' and endogenous opioid release (Benedetti 1996; Montgomery and Kirsch 1997; ter Riet et al 1998; Price et al 1999; Amanzio and Benedetti 1999). Chronic, clinical pain syndromes are complex in nature, with both sensory-discriminative and affective-evaluative components occurring simultaneously (Woolf 1979; Gustin 2011). In these patient populations, a placebo response may indicate that the intervention, in addition to being physiologically effective, may be employed as a coping strategy, reducing affective-evaluative components i.e. pain-related fear and catastrophising or increasing pain self-efficacy (Price et al 1999). Overall, placebo interventions may decrease the level of pain perceived and therefore have the possibility to increased function and quality of life, reducing the burden of the pain and achieving the initial aim of the intervention. This hypoalgesic ability of placebo intervention has been demonstrated within this thesis (Chapter 8). Compared to no intervention, P-TENS was found to increase time to pain tolerance and pain endurance of experimentally induced, lower limb ischaemic pain. Unfortunately, the design of the current clinical study of IC pain does not allow for such a comparison. Active TENS was found to increase walking distance compared to placebo TENS but what is not known is the degree of effect compared to no intervention. Nevertheless, clinical trials of new interventions must be placebo-controlled to determine unequivocal and replicable physiological effects. The current study achieves this for TENS and walking performance in patients with IC. Future research should however aim to quantify the placebo effect and therefore absolute effects of active TENS on walking

performance in patients with PAD and IC. This can be achieved through including a control condition where no intervention is given in addition to the P-TENS control.

---

#### 9.5.2: Frequency parameters of TENS and walking performance:

---

The secondary research question was: does HF-TENS increase measures of walking performance more than LF-TENS? The results of the study suggest that HF-TENS is more effective at increasing walking performance in patients with PAD and IC at lower levels of pain (ICD), but not towards walking tolerance (FCD and ACD).

Median ICD and ACD increased with HF-TENS whereas only FCD and ACD increased with LF-TENS (Table 9.2 and Figure 9.7). Between-group comparison of the median individual change in these measures found that only change in ICD was significantly greater with HF-TENS than with LF-TENS ( $r = 0.49$ ,  $p = 0.038$ ) (Table 9.3). This result suggests that compared to LF-TENS, HF-TENS is more effective at reducing the initial burden of IC pain at threshold levels. When the levels of pain increase however, both types of TENS are effective at prolonging tolerance and therefore increasing walking performance in patients with PAD and IC (Table 9.3 and Figures 9.8 and 9.9).

To reduce the effect of inter-participant differences in walking performance and pain between the groups, individual change in ICD, FCD and ACD was calculated as a percentage of their baseline distance. The group median for each of these measures was then calculated and compared (Table 9.3 and Figure 9.9). Similar to the mean change, the only difference between the groups was in ICD ( $r = 0.49$ ,  $p = 0.037$ ) (Table 9.3). Otherwise, the mean percentage change in the measures was comparable between the groups, indicating that there is no difference between the two selected TENS frequencies in increasing walking distance at near tolerance levels of pain in this population.

These findings relate to those of the within-subject analysis of TENS. HF-TENS appears to be more effective than LF-TENS at reducing the initial perceptions of pain and prolonging time to pain threshold. This has been hypothesised as a function of the more effective electrical

paraesthesia induced with the higher frequency of stimulation eliciting ectopic impulses and abnormal patterns of neural activity (Kiernan et al 1997; Mogyoros et al 2000). The perception of this electrical paraesthesia 'masks' the experience of pain and thus prolongs the time before pain threshold is reported. As LF-TENS does not induce such paraesthesia as effectively and is actually considered to induce an uncomfortable, just below pain threshold stimulation, the limited effects on the initial perceptions of pain are anticipated. An important question however, is what is important, or more effective, for increasing physical activity in patients with PAD and IC? For example, does reducing the initial experience of pain increase daily walking performance or is it more important to prolong the time to tolerance of the pain? No published study has specifically examined when, and why patients with PAD and IC limit their walking distance. Kruidenier et al (2009b) suggested that there is a 'functional claudication distance', individual to every person where they decide to stop walking. This seems to be determined by previous experiences and beliefs regarding the meaning of pain (Kruidenier et al 2009b). This level, as measured in the current study, is similar or near pain tolerance indicating that this is the most important outcome in the evaluation of walking distance in patients with PAD and IC. There was no difference in FCD between the groups although when examining the individual group difference, despite a median decrease, FCD was significantly increased with HF-TENS compared to P-TENS (Table 9.2).

---

#### 9.5.3: Pooled Analysis of TENS:

---

Due to the nature of this small, phase IIa, 'proof of concept' study, a central question was the evaluation of the safety and efficacy of TENS for walking performance in PAD and IC. With this goal in mind, both groups of TENS data were pooled for analysis in an effort to establish the effects of 'TENS intervention' compared to placebo.

TENS was found to be a safe intervention with no adverse events or reactions to the intervention. Compared with P-TENS, ICD, FCD and ACD were found to increase with TENS intervention (Figure 9.10). The primary outcome of the study was ACD as this has been shown to be the most reliable treadmill measure (Nicolai et al 2009b). ACD increased by a

median of 35.5m with TENS intervention ( $p = 0.003$ , Figure 9.10). This result represents a moderate effect of TENS on walking performance ( $r = 0.49$ ) and provides the important groundwork for further study of TENS as an intervention for PAD and IC.

Despite this significant effect of TENS, a large variance was observed in the results, demonstrated by large error bars in Figure 9.10. This large variance indicates that walking distances varied between participants. No further examination of this variance was possible due to the small sample size. However, it indicates a possible limitation of this study. The inclusion criteria required participants to have Fontaine stage II claudication (pain on walking but not at rest) but did not limit participants within a certain distance. This approach to participant recruitment was chosen so that any results from the study could be generalised to a greater population. These decisions regarding selection criteria led to a diverse sample of participants recruited with a mean baseline ACD of 259m but a non-normally distributed and positively skewed range from 99 to 806m (Table 9.1 and Figure 9.7). The results from this pooled analysis of TENS are therefore even more significant considering the effects observed and the inherent variation in the sample. This large variation in walking ability has been encountered before in small studies of patients with PAD and IC (Gardner et al 2008; Serizawa et al 2012) and only studies with greater numbers or more strict inclusion criteria, and thus less generalisation, have overcome this limitation. A larger sample would allow participants to be grouped by baseline walking ability and effects studied within these smaller, more homogeneous populations. Future studies should be aware of this inherent variance within the population and either control for it using inclusion criteria or build in scope for examination when selecting the sample size and statistical analysis.

The change in walking distance with TENS intervention represents an increase in ACD of 20% compared to placebo (Figure 9.10). A change of approximately 37% has been reported as a clinically meaningful change in ACD for patients with IC (De Backer et al 2009). The change with TENS found in the current study falls short of this mark. However, it could be argued that despite this, TENS warrants further investigation. The clinically meaningful difference is



calculated from studies examining longer-term interventions. TENS as an intervention is normally prescribed similar to medication with a view to it becoming integrated within the overall management of a painful condition (Sluka and Walsh 2003; Johnson 2007). Also, establishing optimal dosage of the parameters of TENS has been shown to require a prolonged period of use and personal experimentation (Johnson et al 1991; Johnson 2007). With further refinement of the TENS parameters and if investigated as a long-term intervention rather than an immediate change in behaviour, it is feasible to propose that TENS could achieve this clinically meaningful level of improvement in walking distance.

---

#### 9.5.4: Interrelationships between measures:

---

Bivariate correlation analysis was conducted on the baseline measures to examine any interrelationships. Table 9.4 details the results with the significant relationships highlighted in **bold**. A number of significant correlations were found within the data.

Strong, significant positive relationships were found between the treadmill measures. These results indicate common, proportional differences between ICD, FCD and ACD in patients with IC (i.e. ICD was commonly one third of the distance of ACD). Also, the pattern of pain development over time is generally similar, regardless of the distance walked. This observation indicates similar and consistent mechanisms of pain experience across participants. The proportional relationship between threshold and tolerance of pain, and thus walking distance, suggests a reliable development in pain intensity during walking between participants. Further analysis of individual walking distances showed that an individual's ICD was approximately 40% of their ACD (Mean % (95%CI) = 38 (33-43)). In addition, FCD was found to be 80% of ACD with no intervention = 81% (75-86).

With TENS intervention, these proportions changed slightly. ICD decreased to 35% (29-42) and FCD decreased to 75% (69-82) respectively. These changes may suggest that rather than TENS producing a 'shift' in all aspects of the pain experience, ACD is most affected. As this is only a basic post hoc analysis on preliminary data, further investigation and more comprehensive analysis are required before any conclusions can be drawn. The implication

however, if the observed relationships persist, is that patients with IC walk further with TENS and this is due to an increase at the more severe portion of the pain experience.

The only published study that has examined the IC pain experience and specific hypoalgesic effects during treadmill walking is that by Treat-Jacobson et al (2011). These authors examined the effects of 12 weeks of different exercise interventions (treadmill training, arm ergometry, a combination of both or usual care) on the 'pain trajectory'. A simple 6-point verbal/ numerical rating scale (0 = no pain; 1 = mild claudication pain, onset of pain; 3 = moderate pain; and 5 = severe pain, with no verbal descriptors at points 2 or 4), was used to record immediate pain intensity every 30 seconds during a graded treadmill protocol at the start and end of 12 weeks of the intervention. Due to their method of recording pain intensity, complex analysis and non-reporting of raw data, time taken to pain threshold and tolerance were not available for analysis. The authors' detailed analysis did however indicate a common trajectory of increasing pain over time similar to the current study. Interestingly however, different interventions were found to affect the pain experience in different ways with treadmill training increasing walking time when the pain was most severe and arm ergometry increasing time before the onset of pain (Treat-Jacobson et al 2011). The authors did not speculate or discuss which aspect of the 'pain trajectory' was most important to modify for purposes of increasing function and quality of life in patients with PAD and IC. However, treadmill training resulted in the greatest increase in overall walking time.

Scores on the WIQ were positively related to FCD and ACD. The WIQ is widely used as an outcome measure for studies investigating interventions aimed at improving function in patients with PAD and IC (Matsuo and Shigematsu 2010). In the current study, the relationships observed between WIQ and the treadmill measures indicate that self-reported walking performance is related to actual walking performance on a treadmill. This suggests that the WIQ is a valid tool for measuring walking performance in patients with PAD and IC. Participant WIQ score was related positively to the PSEQ, and negatively to the PCS indicating that there is a relationship between this measure of walking performance and

psychosocial aspects of pain. These results follow the theorised mechanisms suggested in the literature for pain self-efficacy and pain catastrophising (Lorig et al 2001; Edwards et al 2011).

For pain self-efficacy, higher scores on the PSEQ indicate increased confidence in the ability to overcome pain and thus an increase in functional performance. Asghari and Nicholas (2001) found that in a sample of patients with chronic pain, self-efficacy beliefs predicted pain and avoidance behaviours even when controlling for pain severity, pain chronicity, age, gender, physical disability, depression, neuroticism and catastrophising. Specifically, increased pain self-efficacy beliefs were found to be predictive of reduced avoidance behaviours. From the reporting of the study, it was not clear whether the sample examined included patients with IC and therefore, the results cannot be directly extrapolated. Nevertheless, the results of the current study suggest similar relationships are present in this sample of IC pain as an increase in score on the PSEQ was found to relate to an increase in walking performance in patients with IC pain.

Pain Catastrophising can be defined as “an exaggerated negative orientation toward actual or anticipated pain experiences” (Gatchel et al 2007, p602). Higher scores in the PCS indicate higher pain catastrophising, which relates to increased attention to pain and decreased functional performance (Martin et al 1996). To date, no published research has examined the role of catastrophising in patients with PAD and IC. In the current study the negative relationships observed between scores of the PCS and WIQ indicate that an increase in pain catastrophising is related to a decrease in walking performance. Pain catastrophising has been shown to: independently predict depression in a general chronic pain population (Turner et al 2000); is related to increased pain intensity in patients with back pain (Buer and Linton 2002); and in patients with fibromyalgia, pain catastrophising is related to increased activity in the regions of the brain associated with the attention, anticipation and emotional response to pain (Gracely et al 2004). The levels of catastrophising recorded in the current study are similar to those reported in the study by Buer and Linton (2002). A median score of 12 was reported by patients with moderate, 10

with mild and 9 with no back pain (Buer and Linton 2002). In the current study, patients with IC reported a mean score of 12 on the PCS, similar to that of patients with moderate back pain. Due to this similar level of reported catastrophising, it could be assumed that pain catastrophising may have a similar impact for patients with IC as it does for those with back pain. However, unlike in back pain patients, there was no relationship between catastrophising and pain intensity (PRI score) and score of the PCS was not related to measures of walking performance as has been shown in a more general pain population (Turner et al 2000). The only other variables related to PCS were the scores on the PSEQ and TSK. This indicates that rather than a direct relationship with pain and function, the influence of pain catastrophising in patients with IC is mediated through other psychosocial measures.

PSEQ scores were related to the largest number of other variables. Significantly negative relationships were found with BMI, PCS, TSK and PRI scores (Table 9.4). These results indicate that scores on the PSEQ and therefore pain self-efficacy beliefs are related to a large proportion of other variables in this population. The relationships between pain self-efficacy and the other measures in patients with PAD and IC warrants further investigation. Currently, nothing has been published regarding the role of pain self-efficacy in the disease experience of PAD and IC. A number of studies have highlighted general self-efficacy beliefs as an important factor in cardiovascular disease. Relationships have been identified between self-efficacy and cardiovascular lifestyle in general cardiovascular diseases (Sol et al 2011), prescribing habits in patients with PAD (McDermott et al 2010) and walking ability in patients with PAD and diabetes mellitus (Collins et al 2010). In this study by Collins et al (2010), 145 patients with PAD and diabetes were recruited and asked to complete a series of self-report measures including the Self-Efficacy for Managing Chronic Diseases scale. Participant score on this scale was used to divide the sample into those with high or low self-efficacy. This rough dichotomous measure was then found to be related to walking distance on a treadmill, WIQ score and scores of physical functioning quality of life (Collins et al 2010). Due to the method of measurement and analysis, only general relationships could be identified. The results of these studies along with that of the current study suggest

self-efficacy and pain self-efficacy are important mediators of numerous variables and are strongly related to walking performance and function in patients with PAD.

Despite the observed relationships between pain self-efficacy and function in this study, overall pain intensity was not found to relate to measure of walking performance. PRI scores also were not found to be related to any of the treadmill measures or measures of function (Table 9.4). This suggests that rather than physiological measures of the disease, or pain itself, it is the psychological/psychosocial measures associated with the pain experience that are the most strongly related to walking performance and function in this population.

Table 9.5 shows the bivariate correlation coefficients between the measures at baseline and the experimental measures of walking performance with intervention. Of the experimental measures, the only significant relationships were positive and between  $\Delta$ ICD and BMI, and  $\Delta$ ACD and  $\Delta$ mA. The relationship between BMI and  $\Delta$ ICD suggests that patients with a greater BMI had a greater increase in initial walking distance with TENS. The positive relationship between change in ACD and change in TENS intensity suggests that patients who increased TENS intensity to a greater extent through the test had a greater increase in walking distance.

These findings indicate that the participants in this study used TENS as a coping strategy to help them overcome their pain and walk further. Results from this study show that utilising TENS more effectively (i.e. increase the intensity) was related to a greater increase in walking distance. This follows the theory of pain self-efficacy where, if someone believes that they can overcome an obstacle, they are more likely to do things that help them achieve this goal (Bandura 2012). This may suggest that pain self-efficacy could be a predictor of effective use and benefit from TENS. It is beyond the scope of the current study to make these conclusions. Nevertheless, if further research confirms this relationship, this may prove to be an novel avenue for research and may stimulate further clinical questions e.g. if the beneficial effects of TENS are related to pain self-efficacy, should interventions aimed at increasing self-efficacy be implemented along with the provision of TENS units?

There are no published studies that have investigated the relationship between TENS and pain self-efficacy. One study by Luijpen et al (2004) found that TENS increases self-efficacy in patients with cognitive impairments. However, this was general self-efficacy and not related to pain. Future research might look to explore the link between pain self-efficacy and TENS and if present, investigate possible methods that could capitalise on the relationship and enhance the hypoalgesic effects of TENS.

---

#### 9.5.5: Predictors of Walking Performance:

---

The final research questions were: what measures, if any, predict walking performance at baseline and which, if any, predict change in walking performance with intervention? As ACD was the primary outcome of the study, ACD and  $\Delta$ ACD were chosen for the linear models. Enter regression analysis was used to examine which measures most significantly predict baseline ACD and  $\Delta$ ACD.

For the baseline ACD, the model consisted of ABPI, BMI, WIQ and PSEQ. The model entered was a significant fit for that data although no standardised Beta values for individual predictors were found to be significant (Table 9.6). The overall model was found to predict 19% of the variance in ACD. The small, standardised Beta values for BMI or ABPI were not found to be significant and the standard errors in Beta values were large indicating only general relationships with ACD. These findings indicate that scores on the WIQ and pain self-efficacy are the greatest determining factors of walking tolerance measured in this sample of patients with IC.

Table 9.7 shows the results from the regression analysis of  $\Delta$ ACD. Change in TENS intensity was found to be the best predictor of  $\Delta$ ACD. Overall, the model was found to predict approximately 35% of the variance in  $\Delta$ ACD and it was a significant fit for the data.

Again, small, standardised Beta values and large standard errors of these values were observed for the physiological measures indicating only general relationships with the

outcome variable. This was also true for WIQ and PSEQ scores. Conversely, the large standardised Beta value and comprehensive significance of change in TENS intensity observed in this model indicates that it is a strong factor in the overall model with a small change in intensity relating to a large increase in walking distance.

Regression analysis for measures of walking performance at baseline, found the psychological measures of self-reported walking performance and pain self-efficacy to be the best predictors of ACD in this sample of patients with PAD and IC. This indicates that psychological factors associated with pain have a significant impact on the experience of living with PAD and IC, greater than the commonly measured, physiological factors of ABPI and BMI.

Previous published studies have examined the psychological burden of PAD and IC. However, none has examined the effects of the specific psychosocial aspects of the chronic pain experience. The first reported studies to discuss the psychological effect of PAD and IC were Pell (1995), Currie et al (1995), Chetter et al (1997) and Klevsgard et al (1999). Whilst investigating quality of life measures in patients with PAD and IC, these studies noted a relationship between decreased positive psychological variables and Quality of Life (QoL) and walking ability (Klevsgard et al 1999). Chetter and colleagues (1999) investigated and recommended the use of the SF-36 health questionnaire for patients with PAD and IC to help measure and manage the marked decrease in QoL in the population (Chetter et al 1997). Klevsgard et al (1999) examined responses on the Nottingham Health Profile and the Sense of Coherence Scale in 168 patients with IC compared to 102 controls. They found that patients with IC had significantly lower scores on all aspects of quality of life compared to controls. Specifically, measures of pain, physical mobility and emotional reactions were predictive of health status. Sense of coherence, i.e. the resources that allows people to manage tension, reflect on their resources and mobilise them to employ effective coping and find solutions to their health-related issues (Eriksson 2006), was also found to be a mediating factor between physiological severity of ischaemia and quality of life (Klevsgard et

al 1999). This well designed study was the first to suggest this link between psychological beliefs and quality of life in IC, independent of disease severity.

Breek et al (2001) also investigated quality of life in patients with IC. Significantly poorer scores on the domains recording: physical health and level of independence; pain and discomfort; energy and fatigue; mobility, activities of daily living; dependence on medication and treatments; working capacity; negative feelings; recreation and leisure; and overall QoL and general health were recorded in patients with PAD and IC. The authors made a point of noting the limited relationship between walking distance and QoL. A stronger association was found between walking ability and dependence on medication and treatment (Breek 2001).

Further analysis of the relationships between psychological factors and QoL/ function was conducted by McDermott et al (2003) who investigated the relationship between depressive symptoms and lower extremity functioning (6-minute walk distance and walking velocity). They found significant relationships when adjusting for age, sex, race, ABPI, number of comorbidities, current smoking and antidepressant medications. Aquarius et al (2005) examined the effects of disease status and Type D (depressive) personality on outcomes in patients with PAD and IC. Type D personality was found to be associated with increased risk of impaired QoL and perceived stress irrespective of disease status (Aquarius et al 2005). More recently, research has been conducted that further examined the relationship between depression and decreased quality of life in patients with PAD. Smolderen et al (2008) reported that prevalence of depression was high in this sample of PAD patients. Clinical depression was present in 16% of participants and scores on the depression scale were independently related to treadmill walking distance (Smolderen et al 2008). In a separate study the same research group compared the health status and disease burden of PAD to that in Chronic Heart Failure (CHF) (Smolderen et al 2009). Differences were observed between the conditions with increased impairment in physical health in PAD and increased impairment in mental health for patients with CHF (Smolderen et al 2009).



All of these studies highlight a central role of psychological factors, specifically depression, in the physical function and quality of life in patients with PAD. These studies are often cross-sectional 'snapshots' of groups of patients seeking care for their condition so they may not be representative of the whole population or change over time. The study by Smolderen et al (2008) was the only study to perform substantial follow-up. Depressive symptoms were found to be stable over 18 months. In addition, the measure of depression was found to be independently related to walking distance on the treadmill but not to disease severity as measured by the ABPI (Smolderen et al 2008). This suggests that the depressive symptoms observed are related to physical function, and thus possibly the experience of IC pain. Causality is not established however. Depression is a common feature of chronic pain conditions and, along with learned helplessness, has been shown to impact on quality of life and physical function (Keefe et al 2004; Gatchel et al 2007). Similar to patients with PAD and IC, the nature of the relationship between chronic pain and depression is yet to be conclusively established. To date, all studies of depressive symptoms in patients with PAD have been conducted on participants who also experience claudication. To begin to further examine the relationship between PAD, IC and depression, future research could explore the same symptoms in patients with asymptomatic PAD with long-term follow-up to investigate how these symptoms relate to the development of IC pain.

Despite this acknowledgement of the role of psychological well-being and PAD, published qualitative literature that explores the intricacies of psychological aspects of PAD and IC is minimal and there is only one study found to date that investigates the effects of psychological intervention for PAD and IC (Cunningham et al 2011). In a well-designed RCT, patients with IC who received brief psychological intervention (2, one-hour sessions where illness and walking beliefs were addressed and a personalised action plan agreed upon) were found to have increased total number of steps per day at the four-month follow-up compared to those who received normal care (Cunningham et al 2011). Similar to the current study, this trial highlights the major limiting function of psychological factors and how a simple, low-cost intervention can increase walking distance.

Qualitative research has examined the barriers and facilitators for walking in patients with PAD and IC (Galea et al 2008). Barriers included lack of energy, fatigue, lack of motivation, perceived time constraints, lack of knowledge and uncertainty regarding benefits of walking, exercise-induced pain, the need to take breaks due to pain and confusion about the benefits and harm caused by pain. The facilitators identified were psychological strategies such as goal setting and positive self-talk, social support, cognitive and behavioural pain-coping strategies, the availability of walking programs and the availability of a resting place when walking. Again, these results support the current findings and highlight the role of pain, and more specifically the psychological aspects of the pain experience as major determinants of walking adherence and/or performance in patients with PAD and IC.

The findings of facilitators such as motivation, goal setting, positive self-talk and coping strategies are all features associated with self-efficacy (Bandura 2012) as are the barriers reported by Galea et al (2008) of uncertainty about the benefits of walking. The confusion about the benefits and harm caused by pain are features related to pain-related fear and avoidance behaviours (Vlaeyen et al 1995). The results of the current study therefore seem to support those of the study by Galea et al (2008). Future studies could investigate these barriers and facilitators in further depth to gain a better understanding of walking in this population. This information could then be used to develop and test interventions for promoting physical activity and walking performance.

Previous research has shown that there is a strong association between PAD and decreased QoL/health status. This link has been found to be more closely related to psychological than physiological or physical measures. The current study adds to these conclusions by suggesting a specific effect of psychosocial aspects of the pain experience on walking performance. Further research should examine this link further with the aim of identifying the psychological constructs that have the greatest effect on physical function and QoL in PAD and IC. Once identified, interventions that target these specific constructs may be able to be designed with the ultimate aim of increasing QoL in this patient population.

## 9.6: CONCLUSIONS:

---

Patients with IC experience a gradual build-up of pain to tolerance when exercising. This is similar to the ischaemic pain curve discussed earlier (Chapter 8) and the distinct aspects of this pain experience are used to quantify walking performance. Pain threshold (ICD) and pain tolerance (FCD/ACD) are used as outcomes.

The current study aimed to investigate the effects of two types of TENS (high and low frequency) on the pain experienced and walking performance in patients with PAD and IC. The results indicate that TENS increases the distance walked before tolerance. Both types of TENS were found to increase walking performance although HF-TENS was more effective at prolonging time to pain threshold.

TENS increases treadmill walking performance in patients with PAD and IC with change in stimulation intensity being the best predictor of change in walking distance.

## 9.7: CHAPTER 9 SUMMARY:

---

To investigate the effects of TENS for IC pain, 40 participants with PAD and IC were recruited to this phase IIa study. Participant walking performance and report of pain during the Gardner treadmill test with either HF or LF-TENS was compared to that with placebo TENS.

The main finding of this preliminary study is that compared to placebo, walking tolerance distance (ACD) increased with both HF and LF-TENS stimulation. ICD and FCD also increased with HF-TENS. However, no differences in ICD or FCD were observed with LF-TENS.

The only observed difference between the groups was for ICD. The difference in walking distance with TENS intervention was greater with HF-TENS compared to LF-TENS. When the data for both groups was pooled, TENS was found to increase all measures of walking performance compared to placebo. When examining change in ACD using multiple linear regression, participant-controlled change in intensity of TENS stimulation was the only variable found to significantly predict a change in ACD.

In conjunction with the laboratory study of TENS for lower limb ischaemic pain described in Chapter 8, the results of this study fulfil the aim of this thesis: to investigate the hypoalgesic effects of TENS on lower limb ischaemic pain and walking performance in patients with IC. TENS appears to be an effective intervention in reducing the perceived intensity of ischaemic pain and increasing walking distance. The current studies are however, preliminary and thus further investigation of TENS for IC is required prior to its acceptance as a useful adjunctive intervention for PAD and IC.

## CHAPTER 10: COMPARISON OF EXPERIMENTAL AND CLINICAL ISCHAEMIC PAIN

---

### 10.1: AIM OF CHAPTER 10:

---

In Chapter 8 the hypoalgesic effects of TENS on mSETT induced ischaemic pain in the lower limb of healthy volunteers was established. Chapter 9 reported similar findings in a sample of patients with IC pain walking on a treadmill. The mSETT model of laboratory ischaemic pain was used as a pre-clinical model of IC pain due to its apparent face validity: inducing ischaemic pain in the lower limb. What is not known however is whether the pain experience induced by the mSETT is similar to that of clinical IC.

The subjective qualities of the experience of IC pain have not been fully explored in the literature. Thus, comparison of pain induced by the mSETT with clinical IC pain is limited. During the studies reported in Chapters 8 and 9, descriptions of pain were recorded using the MPQ. This chapter will describe and discuss the preliminary exploration of these descriptions of pain. The subjective qualities of pain reported by patients with IC pain will be compared with those reported by healthy volunteers with the mSETT. The analysis aims to examine similarities and differences in the pain experienced. Three concepts were examined: 1) the descriptive qualities of the pain, 2) the intensity of these qualities and 3) the overall pain experience.

The aim of this chapter is therefore to analyse and compare the pain experience recorded during the studies described in Chapters 8 and 9. This analysis will contribute to addressing the aim of the thesis: to investigate the subjective description of the multidimensional qualities of ischaemic pain. If achieved, this improved understanding of the experience of lower limb ischaemic pain could inform future examinations of the impact of lower limb ischaemic pain and interventions of possible management strategies for IC.

## 10.2: METHODS:

---

### 10.2.1: Design:

---

This is a post-hoc analysis of data gathered in two previous studies (described in Chapters 8 and 9). Data gathered during the experiments was aggregated with the different studies forming two groups (clinical and laboratory). An analysis was conducted on the MPQ descriptions of the pain experienced by patients with IC when walking on a treadmill and healthy volunteers during the mSETT.

### 10.2.2: Participants:

---

Thirty-six patients with IC made up the clinical group and twenty-seven healthy volunteers comprised the laboratory group. Recruitment and inclusion/exclusion criteria were as previously described (Chapters 8 and 9).

### 10.2.3: Study Procedure:

---

Patients with IC completed a standardised treadmill test. Healthy volunteers completed the mSETT. Five minutes following testing, participants completed the MPQ administered by the researcher.

### 10.2.4: Measures:

---

Participants were asked to describe the pain they experienced at pain tolerance using the vocabulary of the MPQ.

### 10.2.5: Statistical Analysis:

---

Data were collated, graphed and analysed for similarities and differences between the groups focussing on the central concepts of descriptive quality, intensity, and overall pain experience.

To examine the descriptive quality of the two pain experiences, the Number of Words Chosen (NWC) and percentage utilisation of MPQ subclasses were calculated for both groups. A cut-off of greater than 50% utilisation was selected as an indication of agreement

amongst the participants (Chen and Treede 1985). More than 50% utilisation was selected, as this would indicate that the majority of participants in the group felt that an adjective from that subclass adequately represented a part of the pain experience.

The intensity of the experience was explored through the ranks of adjectives in the subclasses with more than 50% utilisation. Using the method described by Melzack et al (1985), the weighted-rank of adjectives chosen was calculated and compared between the groups (Jerome et al 1988; Strong 1999). For an overall assessment of the pain experience, Pain Rating Index (PRI) scores were calculated and compared (Melzack et al 1985; Chen and Treede 1985; Jerome et al 1988; Strong 1999). These data were normally distributed ( $p > .05$  on Shapiro Wilk test) therefore independent student's t-tests were used to compare the scores between the groups.

Statistical significance was set at  $p = 0.05$  (two-tailed). Analysis was performed using SPSS version 19.0.

### 10.3: RESULTS:

#### 10.3.1: Participants:

The participants were 36 patients with IC and 27 healthy volunteers. The groups differed in age (Table 10.1).

Table 10.1: Participants included in the analysis with clinical or induced ischaemic pain.

	Clinical	Laboratory
<b>Number of Participants</b>	36	27
<b>Mean Age (range)</b>	68 (53-85)	26 (18-45)

#### 10.3.2: Descriptive Qualities:

The Number of Words Chosen (NWC) of the MPQ is a general measure of pain description. NWC can provide an overall indication of the severity and descriptive qualities of pain. In the current study, participants in both groups selected similar numbers of words to describe the pain experience (Table 10.2). The mean total NWC in the laboratory group was greater than that in the clinical group. This greater number of words chosen was not limited to one sub-dimension of the MPQ with similar proportional differences between the groups in sensory and reactive subclasses (Table 10.2).

Table 10.2: Mean (SE) NWC in each group.

	Clinical	Laboratory
<b>Total</b>	9.1 (0.64)	10.8 (0.58)
<b>Sensory</b>	4.9 (0.34)	5.6 (0.31)
<b>Reactive</b>	4.2 (0.38)	5.1 (0.32)

NWC provides an overall indication of questionnaire utilisation between the groups. The next part of the analysis aimed to examine whether the words chosen to describe the pain experience in both groups came from similar subclasses and thus described similar qualities of pain.



Subclass utilisation was similar in both groups. Seven subclasses were utilised by greater than 50% of participants in the clinical group (1, 5, 9, 11, 16, 18 and 20) (Figure 10.1). The majority of laboratory participants also utilised the same subclasses. However, they also frequently utilised four other subclasses (7, 8, 14 and 17) (Figure 10.1).

---

#### 10.3.3: Intensity:

---

Table 10.3 displays the subclasses and adjectives of the MPQ along with their classifications and rank. Highlighted by shading and with an asterisk are the subclasses with more than 50% utilisation by clinical participants. The rank of adjective indicates its intensity compared to the other adjectives in the same subclass. In an effort to identify and compare the perceived intensity between groups the most commonly chosen adjective (mode adjective) was identified for each subclass with more than 50% utilisation in both groups (Table 10.4). The most frequently chosen adjective was the same for each group in three of the seven subclasses. For the other four subclasses, laboratory participants more commonly selected a higher rank of adjective than the clinical group (Table 10.4).

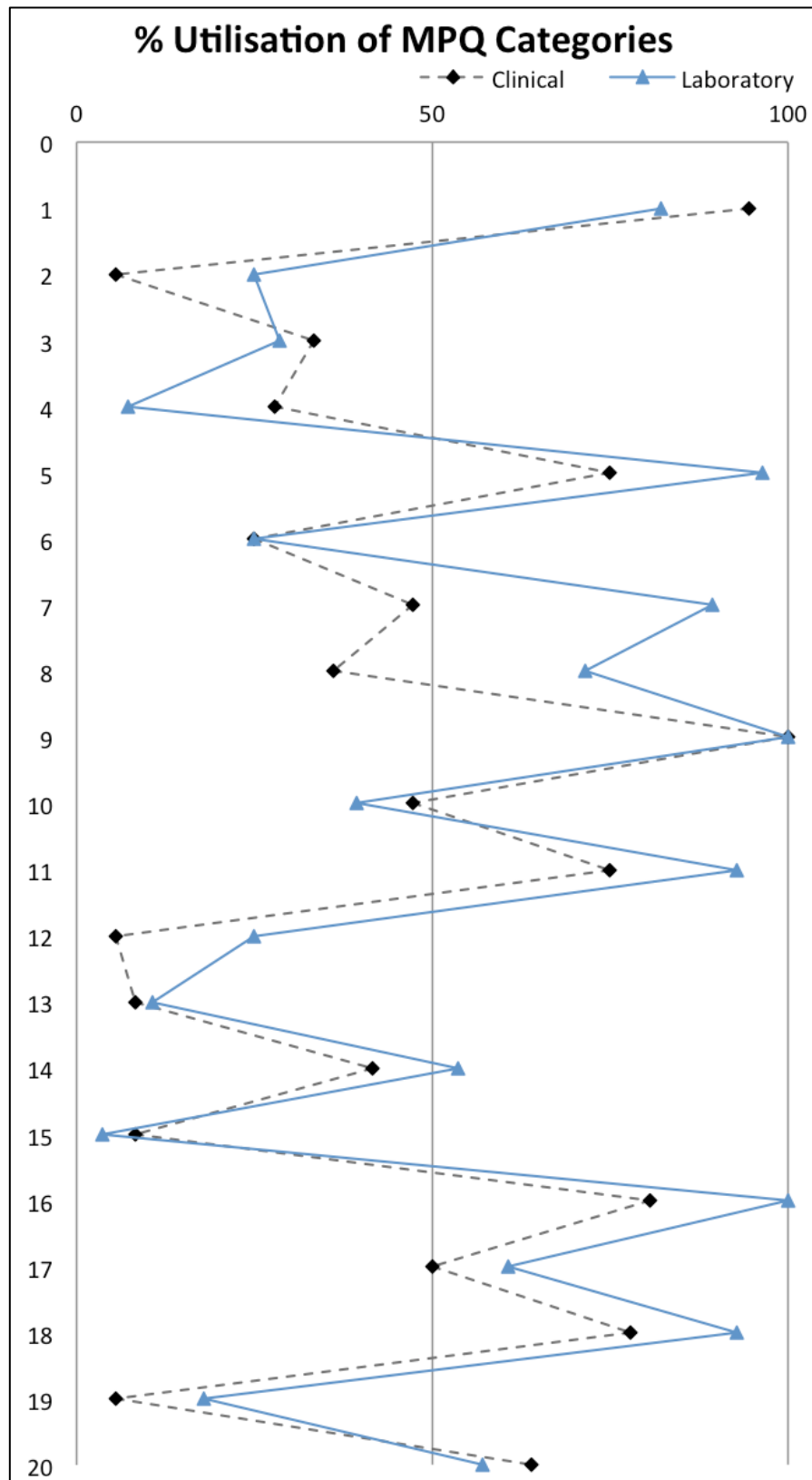


Figure 10.1: Graph of percentage utilisation of MPQ subclasses in Clinical and Laboratory participants.

Table 10.3: Classification of subclasses and ranked adjectives included in the MPQ. Subclasses highlighted by shading and an \* are those with more than 50% utilisation by the clinical group.

Subclass	Adjectives and Rank					
	1	2	3	4	5	6
1 Temporal*	Flickering	Quivering	Pulsing	Throbbing	Beating	Pounding
2 Spatial	Jumping	Flashing	Shooting			
3 Punctuate pressure	Pricking	Boring	Drilling	Stabbing	Lancinating	
4 Incisive Pressure	Sharp	Cutting	Lacerating			
5 Constrictive pressure*	Pinching	Pressing	Gnawing	Cramping	Crushing	
6 Traction Pressure	Tugging	Pulling	Wrenching			
7 Thermal	Hot	Burning	Scalding	Searing		
8 Brightness	Tingling	Itchy	Smarting	Stinging		
9 Dullness*	Dull	Sore	Hurting	Aching	Heavy	
10 Sensory Miscellaneous	Tender	Taut	Rasping	Splitting		
11 Tension*	Tiring	Exhausting				
12 Autonomic	Sickening	Suffocating				
13 Fear	Fearful	Frightful	Terrifying			
14 Punishment	Punishing	Gruelling	Cruel	Vicious	Killing	
15 Affective-evaluative-sensory miscellaneous	Wretched	Blinding				
16 Evaluative*	Annoying	Troublesome	Miserable	Intense	Unbearable	
17 Sensory-miscellaneous	Spreading	Radiating	Penetrating	Piercing		
18 Sensory-miscellaneous*	Tight	Numb	Drawing	Squeezing	Tearing	
19 Sensory	Cool	Cold	Freezing			
20 Affective-evaluative miscellaneous*	Nagging	Nauseating	Agonising	Dreadful	Torturing	

Table 10.4: Mode adjective chosen in subclasses with more than 50% utilisation in both groups. Classification of subclasses is also included. Note the higher rank of word chosen in the laboratory group for categories 1, 9, 11 and 16 (highlighted in **bold**).

Classification	Subclass	Mode Adjective	
		Clinical	Laboratory
Sensory	1.Temporal	Throbbing	<b>Pounding</b>
	5.Constrictive Pressure	Cramping	Cramping
	9.Dullness	Aching	<b>Heavy</b>
Affective	11. Tension	Tiring	<b>Exhausting</b>
Evaluative	16. Evaluative	Troublesome	<b>Unbearable</b>
Miscellaneous	18. Sensory-Miscellaneous	Tight	Tight
	20. Affective-Evaluative-Miscellaneous	Nagging	Nagging

#### 10.3.4: Overall pain experience:

The Pain Rating Index (PRI) score of the MPQ provides an overall measure of pain intensity. There are two different interpretations of the score: PRI Scale (PRI (S)) and PRI Rank (PRI (R)). The PRI (S) is the sum of all the ranks of each adjective whereas the PRI (R) is the sum of weighted adjective ranks as previously described (Melzack et al 1985). For the current analysis, both measures will be examined.

##### 10.3.4.1: PRI (S)

All PRI (S) data are displayed in Table 10.5. Mean Total PRI (S) scores in the clinical group were significantly lower than the laboratory group. Similar findings were evident for both sensory and reactive subclasses (Table 10.5).

##### 10.3.4.2: PRI (R)

Mean Pain Rating Index Ranked (PRI (R)) scores followed a similar pattern with laboratory participants reporting higher overall pain intensity (Table 10.5). Significant differences were found for total, sensory and reactive scores.

When examining the mean weighted-rank of adjective chosen, the difference in PRI scores can be seen to be the result of a lower rank of word chosen in the majority of subclasses by

participants in the clinical group (Figure 10.2). Apart from subclasses 3, 8, 10, 17 and 19, the mean weighted-rank of adjective chosen was greater in the laboratory group (75% of the total subclasses). In addition, for all subclasses with more than 50% utilisation in both groups, the mean weighted rank of adjective was greater in the laboratory group (1, 5, 9, 11, 16, 18 and 20) (Figure 10.2).

Table 10.5: Mean (SE) PRI scores for both groups. Statistics represent independent student's t-tests (two tailed).

		<b>Clinical</b>	<b>Laboratory</b>	<b><i>t</i> (62)</b>	<b><i>p</i></b>	<b>95% CI</b>	<b><i>r</i></b>
<b>PRI (S) Score</b>	<b>Total</b>	21.25 (1.32)	29.00 (1.83)	3.517	.001	3.4-12.2	.41
	<b>Sensory</b>	14.47 (0.82)	17.43 (1.05)	2.259	.027	0.3-5.6	.28
	<b>Reactive</b>	6.78 (0.71)	11.57 (0.93)	4.179	.000	2.5-7.1	.47
<b>PRI (R) Score</b>	<b>Total</b>	20.03 (1.49)	28.21 (2.03)	3.330	.001	3.3-13.1	.39
	<b>Sensory</b>	11.75 (0.80)	14.46 (0.93)	2.228	.030	0.3-5.2	.27
	<b>Reactive</b>	8.22 (0.91)	13.57 (1.21)	3.606	.001	2.4-8.3	.42

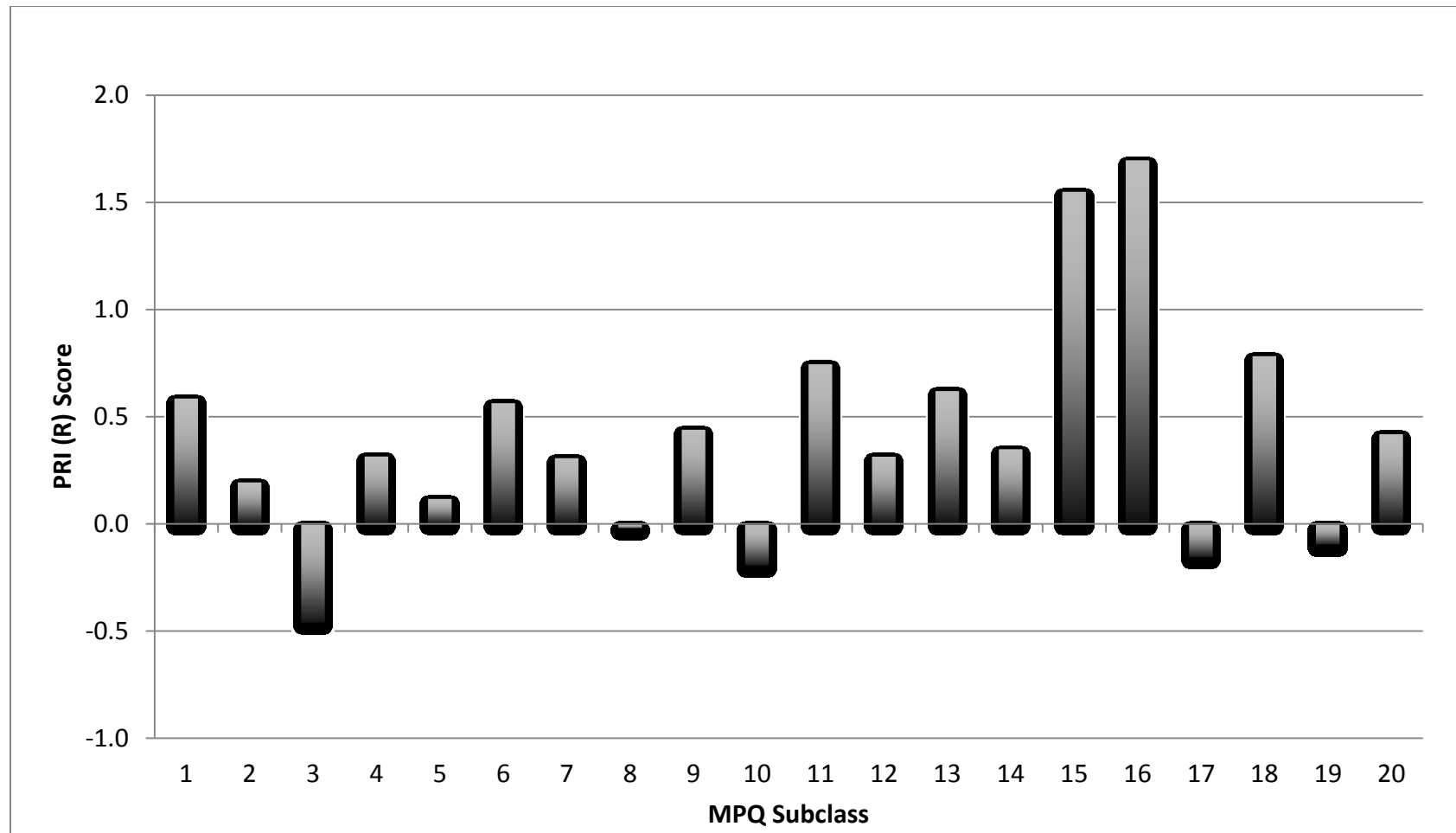


Figure 10.2: Graph of the difference in mean PRI (R) scores between the groups for all subclasses. Positive scores indicate subclasses where the mean PRI(R) scores were greater in participants experiencing experimental ischaemic pain.

#### 10.4: DISCUSSION:

---

The pain experience associated with IC has not been fully explored in the literature. This study provides the first comparison of clinical and experimental ischaemic pain in the lower limb. The results of this study suggest that ischaemic pain is a complex, multi-dimensional experience although a few key qualities appear to emerge.

---

##### 10.4.1: IC Pain:

---

The first objective of this study was to provide a comprehensive description of the subjective qualities of IC pain. The most commonly selected adjectives to describe clinical IC pain were (in descending order): ‘aching’, ‘throbbing’, ‘troublesome’, ‘tight’, ‘cramping’, ‘tiring’ and ‘nagging’. This represents 3 sensory (aching, throbbing and cramping), 1 affective (tiring) and 3 evaluative or miscellaneous (troublesome, tight and nagging) subclasses. The three sensory adjectives chosen to describe the pain experience suggest a nociceptive pain experience related to an ischaemic environment (Lang et al 2009). These correlate with the words used to anecdotally describe IC in the clinical literature (Olin et al 2010).

Rüger et al (2008) investigated the pain experience associated with chronic ischaemia in the lower limbs of patients with PAD. One hundred and two participants were recruited with varying degrees of PAD (61 with Fontaine stage II and 41 with stage III or IV) from an inpatient ward in a large teaching hospital. These authors employed a number of questionnaires including the Short Form McGill Pain Questionnaire (SF-MPQ) with the aim of recording the subjective nature of the pain experience. The sensory descriptors ranked highest by participants with IC were ‘stabbing’, ‘cramping’ and ‘aching’. The only affective descriptor to be ranked highly was ‘tiring-exhausting’. In participants with Chronic Limb Ischaemia (CLI), sensory descriptors of ‘stabbing’, ‘hot-burning’ and ‘tender’ along with affective descriptors ‘tiring-exhausting’ and ‘punishing-cruel’ were ranked highest (Rüger et al 2008) (Table 10.6). Quality of pain is similar between the current study and that of Rüger et al (2008) and across the sub-groups (CLI, IC and Healthy volunteers). Further analysis is limited due to the different measures employed. The SF-MPQ does not allow the choice of

all the adjective present in the original MPQ. The results of the study by Rüger et al (2008) for describing the qualities of ischaemic pain are therefore limited.

Sensory adjectives describing constrictive pressure (cramping) and dullness (aching) were highlighted in both studies. The punctuate pressure adjective of 'stabbing' was rated highly by patients in the study by Rüger et al (2008) although this was utilised by less than a third of participants in the current study (Figure 10.2). Temporal sensations (throbbing/pounding) were common amongst healthy volunteers and those with IC in the current study. However, they were not chosen frequently in the previous study (Rüger et al 2008). Healthy volunteers chose 'thermal' and 'brightness' descriptors. Adjectives 'hot' and 'tingling' were selected most frequently in the current study but this finding was only repeated in the CLI sample of Rüger et al (2008) (hot-burning) (Table 10.6).

The affective dimensions of ischaemic pain seem to be focussed on 'tension' (tiring/exhausting) and 'punishment' (punishing-cruel/ gruelling). These factors were highlighted in both studies with punishment exclusively linked with CLI and laboratory-induced ischaemic pain (Table 10.6).

The SF-MPQ does not include evaluative or miscellaneous subclasses and therefore comparison with the current study is limited. The current study highlighted three specific evaluative and miscellaneous subclasses that may be integral to the ischaemic pain experience. The evaluative subclass of the MPQ was utilised by 81% of patients with IC and 100% of healthy volunteers in the current study. The rank of adjective however, was different indicating different intensity between the groups. Patients with IC most commonly chose the word 'troublesome' whereas healthy volunteers selected 'unbearable'. This may be a reflection of the temporal aspect of the two pain experiences i.e. the chronic nature of IC compared to the acute, transient nature of mSETT-induced pain. Patients with IC are more accustomed to the pain and therefore see it as annoying but have learnt to manage it effectively. Healthy volunteers, who are experiencing a new pain experience, may not know what to expect and thus may evaluate the experience as being more severe.



Other subclasses that were commonly utilised by participants in the current study were those that represent sensory-miscellaneous and affective-evaluative-miscellaneous (Table 10.6). Over three quarters of patients with IC and healthy volunteers selected an adjective from subclass 18 with ‘tight’ being the most frequently chosen in both groups. Descriptors ‘nagging’ and ‘spreading’ were similarly commonly utilised by both groups although less frequently (approx. 60 and 50% utilisation respectively).

Table 10.6: Summary of the current descriptions of ischaemic pain in the literature compared with the results from the current study. Reported here are the highest ranked descriptors from the SF-MPQ (Rüger et al 2008) and the most commonly utilised adjectives from the MPQ (Current Study).

<b>Study</b>	<b>Rüger et al (2008)</b>		<b>Current Study</b>	
<b>Sample</b>	IC (n=61)	CLI (n=41)	IC (n=36)	mSETT (n=27)
<b>Measure</b>	SF-MPQ	SF-MPQ	MPQ	MPQ
<b>Sensory Descriptors</b>	Stabbing	Stabbing	Throbbing	Pounding
	Cramping	Hot-Burning	Cramping	Cramping
	Aching	Tender	Aching	Hot
				Tingling
<b>Affective Descriptors</b>				Heavy
	Tiring-exhausting	Tiring-exhausting Punishing-cruel	Tiring	Exhausting Gruelling
<b>Evaluative/ Miscellaneous Descriptors</b>			Troublesome	Unbearable
			Spreading	Spreading
			Tight	Tight
			Nagging	Nagging

From this general analysis, ischaemic pain due to claudication is characterised by a sensory experience of ‘aching’ and ‘cramping’ along with feelings of tiredness and fatigue contributing to the affective component. These descriptors are similar to those described in other nociceptive pain experiences (Wilkie et al 2001; Dobratz 2008) and suggest afferent c-fibre activity related to tissue ischaemia (Hiatt 2001). The experience of healthy volunteers

with induced ischaemic pain and patients with CLI is slightly different. Additional, and different sensory aspects are described including 'stabbing' and 'hot' along with the affective aspect of punishment. This suggests a different, or additional aspect to the pain experience. Rüger et al (2008) hypothesised a neuropathic component of the pain experienced by patients with CLI associated with long-term ischaemia affecting perfusion of neural tissues. The findings in the current study with healthy volunteers appear to indicate similar mechanisms. The method of inducing ischaemia using a pneumatic cuff has been shown to produce ischaemia in peripheral tissues and thus must be reducing blood flow to peripheral tissues (Roche et al 2007; Seenan et al 2008). The results of the current study may suggest however that the mSETT method induces too much occlusion to be comparable to the IC pain experience. Patients with IC have varying degrees of lower limb vessel occlusion although not enough reduction in blood flow to cause pain at rest. By using a cuff inflated to 200mmHg (at least 60mmHg above any participant's systolic blood pressure), a greater degree of occlusion of blood vessels may have been achieved. In addition to a greater restriction of blood flow, the neural tissues are likely to be compressed due to the general pressure produced by the pneumatic cuff (Sato et al 2012).

Dubuisson and Melzack (1976) classified a number of pain syndromes by their 'descriptive clusters' from the MPQ. By highlighting any adjective chosen by more than 33% of participants, they identified important adjectives that classify specific pain experiences. Applying the same analysis to the data in the current study, core sets of adjectives are identified for IC pain and experimental ischaemic pain (Table 10.7). These 'clusters' are similar to those identified with the previous analysis (Table 10.6) that followed the analysis employed by Chen and Treede (1985). Overall, the resulting clusters of adjectives are not too dissimilar. For IC pain, the sensory adjective 'hot' was added to the list and the evaluative adjectives 'troublesome' and 'spreading' were removed. In the sample of healthy volunteers describing experimental ischaemic pain, the sensory adjective 'tingling' is removed; the affective adjective 'tiring' added; the evaluative adjective 'nagging' removed and the miscellaneous adjective 'squeezing' added (Table 10.7).

Table 10.7: Summary of the results from the two different methods of analysis.

<b>Analysis</b>	Mode adjective in subclasses with >50% utilisation		Adjective with >33% utilisation overall	
<b>Sample</b>	IC (n=36)	mSETT (n=27)	IC (n=36)	mSETT (n=27)
<b>Sensory Descriptors</b>	Throbbing Cramping Aching	Pounding Cramping Hot Tingling Heavy	Throbbing Cramping Hot Aching	Pounding Cramping Hot Heavy
<b>Affective Descriptors</b>	Tiring	Exhausting Gruelling	Tiring	Tiring Exhausting Gruelling
<b>Evaluative/ Miscellaneous Descriptors</b>	Troublesome Spreading Tight Nagging	Unbearable Spreading Tight Nagging	Tight Nagging	Unbearable Spreading Tight Squeezing

When following the analysis of Dubuisson and Melzack (1976) the descriptive clusters of adjectives are similar, yet unique, when compared with other pain syndromes (see Table 3.2 in Chapter 3). IC pain shares some sensory adjectives with back, arthritic and menstrual pain but is unique in the inclusion of 'hot'. For affective adjectives, 'tiring' is commonly used to describe menstrual, labour and back pain. The evaluative and miscellaneous adjectives used to describe IC pain are not included in the clusters describing the pain syndromes examined by Dubuisson and Melzack (1976).

IC pain therefore appears to be a unique pain experience, characterised by specific sensory, affective and evaluative adjectives. In terms of pain intensity, IC pain has not previously been quantified. Melzack (1984) collated PRI scores of the MPQ, recorded in different clinical pain syndromes with the aim of comparing severities. In the current study, a mean PRI score of 21.25 was recorded for IC pain (Table 10.5). Using the data reported by Melzack (1984) this places IC pain above toothache, arthritis and fracture pain but below labour, back, cancer and phantom limb pain. No real conclusions can be drawn from this arbitrary ranking of pain syndromes, which are all complex, multifaceted and unique to the individual.

However, it does indicate that IC pain is an intense experience and worth further investigation.

Studies conducted to date indicate that the ischaemic pain experience is one characterised by specific sensory, affective and evaluative perceptions. Sensory-discriminative components focus on adjectives of ‘cramping’, ‘aching’ and ‘stabbing’; affective-motivational components ‘tiring’ or ‘exhausting’ and cognitive-evaluative components ‘spreading’, ‘tight’ and ‘nagging’ (Table 10.6 and 10.7). This is comparable to other pain experiences in quality and intensity although it has its own unique features. This study provides a small but important initial step towards a comprehensive description of the experience of IC pain.

---

#### 10.4.2: Clinical and Laboratory-Induced Ischaemic Pain:

---

The second objective of this study was to examine the qualitative experience of experimentally induced ischaemic pain in the lower limb of healthy volunteers. This description was then compared with the descriptions of the experience of IC in an effort to evaluate the possibility of using the mSETT method of inducing ischaemic pain as a model of IC pain for pre-clinical testing of analgesic interventions.

The most commonly selected adjectives to describe experimental ischaemic pain were: ‘heavy’, ‘unbearable’, ‘cramping’, ‘exhausting’, ‘tight’, ‘hot’, ‘pounding’, ‘tingling’, ‘spreading’, ‘nagging’ and ‘gruelling’. Comparing these adjectives to those chosen by patients with clinical ischaemic pain, the pain experience induced by the mSETT seems to be a mixture of that associated with IC and more severe CLI (Table 10.6). The sensory subclasses representing temporal, constrictive pressure and dullness were commonly utilised, similar to the pain experience of IC. However, thermal adjectives, uniquely selected to describe the CLI pain experience, were commonly selected to describe mSETT-induced pain (Table 10.6). A similar pattern was reflected in the affective subclasses. All populations selected adjectives relating to ‘tension’ (tiring/exhausting) although participants with either CLI or mSETT pain uniquely selected adjectives from the subclass representing ‘punishment’

(punishing/gruelling) (Table 10.6). These findings indicate that the mSETT induces pain that is more intense than IC pain and more like that experience by patients with CLI.

Similar conclusions can be drawn from the analysis of PRI scores. Mean PRI scale, and mean PRI rank scores with mSETT were significantly greater than with IC pain (Table 10.5). For the mSETT to be utilised as a pre-clinical model of IC pain, it must induce a comparable quality and intensity of pain. The perceived intensity of a pain experience can be defined by sensory, affective and evaluative components (Melzack and Casey 1968). These components are interdependent and relate to the individual perception and experience of a situation. A strength of the current study was the use of the full MPQ that aims to measure these components of the pain experience and thus indicate where modifications can be made to more closely align the pain experiences of the mSETT and clinical IC. Differences were observed between the reported experiences in each of the three components (Table 10.6). This indicates that there may be multiple factors accounting for the observed differences in overall experience.

In terms of sensory experience, adjectives that were either equally, or more intense were selected to describe mSETT compared to IC pain (Table 10.6). These findings may suggest a more severe ischaemic environment experienced with the mSETT procedure compared to that of IC. The ischaemic environment experienced during the mSETT is determined by the parameters chosen so small changes in the mSETT procedure could change the pain experience to more accurately reflect that of IC. This could be achieved through a reduction in the number of repetitions or the amount of force required in the submaximal exercise; a reduction in the pressure in the pneumatic cuff or the degree of pressure that the participants are required to maintain through the leg being tested. By changing the mSETT procedure, the sensory experience of IC pain may be more closely matched.

For the affective and evaluative components of the pain experience, it may be more challenging to attempt to match the experiences. The affective and evaluative components relate to an individual's mood, motivation, attitudes, beliefs and past experiences and these

are not as easily manipulated. Fundamentally, the two experiences are somewhat different. The mSETT is an acute, transient, laboratory-induced pain in healthy volunteers and IC is a chronic, illness-related pain experience in a generally elderly population. Due to these inherent differences in situation and therefore meaning of the experience for the participant, the affective and evaluative components will naturally be dissimilar. The higher rank of affective words chosen by participants describing the mSETT may be related to a greater degree of attention directed towards the 'novel' pain experience compared with patients with IC, who have daily leg pain. This relates to the 'interruptive' nature of pain (Eccleston and Crombez 1999) where pain is selected as cue to urge escape from a dangerous situation. If the pain has been experienced repeatedly over time, this urge to escape may have been suppressed: learning has occurred and the stimulus is now interpreted as 'not dangerous' and thus the affective response is reduced (Eccleston and Crombez 1999; Moore et al 2012). This obstacle is not likely to be overcome in laboratory setting. Even if the healthy volunteers were subjected to repeated tests to acclimatise them to the experience it would still not reflect the multifaceted experience of living with a chronic disease such as IC that causes daily pain and limits most daily activities (Gibson and Kenrick 1998; Wann-Hansson et al 2008; Egberg et al 2012).

A laboratory pain model will not be able to reflect the unique feelings and emotional response of the clinical pain syndrome. The central aim of a laboratory model is to reduce the confounding variables associated with the clinical condition so that the effects of interventions on the common, physiologically driven, sensory experience can be studied. With this in mind, future study should focus on manipulating the sensory experience to match that reported in patients with IC.

The mSETT induces a pain experience comparable to IC. It is established however, that clinical pain syndromes are complex and multidimensional with sensory, affective and evaluative components occurring simultaneously (Woolf 1979). These factors make patients with clinical pain syndromes less than ideal subjects for initial investigations into the efficacy of potential analgesics (Staahl and Drewes 2004). Clinically, patients often have confounding

co-morbidities and are likely to be taking some form of medication and may interpret other effects of the intervention, e.g. effect on anxiety or depression relating to the disease, as a relief of pain (Staahl and Drewes 2004). Experimental pain however, affords a degree of control over these possibly confounding variables and thus is used to study pain, its consequences and the effects of interventions. Consequently, the nature and purpose of an experimental pain method is not to mirror clinical pain in all its components; as if it did, it would not be fulfilling its purpose of eliminating the erroneous variables associated with clinical pain. What might be expected is for experimental pain to be similar in sensory experience. The current study demonstrates this function for the mSETT. The sensory experience is similar to that experienced with IC pain, and with further refinement may become even closer. The mSETT can therefore be seen as a suitable pre-clinical model of IC pain.

---

#### 10.4.3: Limitations to this Approach for Validation of the mSETT:

---

This study addressed two objectives of the research programme: to investigate the subjective description of ischaemic pain and to perform an initial validation of the mSETT as a pre-clinical model of IC pain. These objectives were successfully achieved. However, there are important limitations that must be acknowledged.

One factor to consider is the age of the participants included. The clinical sample had a mean age of 68 years whereas the sample of healthy volunteers had a mean age of 26 years. Gagliese and Melzack (2003) have identified that report of the quality of pain changes with age. A number of reasons for this difference have been speculated upon. It has been suggested that due to the increased chance of experiencing pain as a consequence of age, reports of pain reduce as it is seen as normality. The difference may also be attributed to normal age-related changes within brain tissue or a different understanding of the words employed within the MPQ (Gagliese and Melzack 2003). Regardless of the possible reasons, it presents a limitation of this study, as the clinical sample is considerably older than the healthy volunteers. This introduces inherent differences in reports of pain quality and thus

reduces the power of the comparison of pain experiences. Future studies could aim to match participants on age between samples.

Another limitation of this study is the circumstance in which the clinical pain was recorded. MPQ descriptions of pain were completed immediately after a maximal treadmill test. This test is not something this group of patients complete on a regular basis and their normal experience of pain is during everyday walking activities. For the purposes of this study, it was important that this method was employed to ensure some parity of stimulus between participants. This also allowed for a possibly more valid pain experience to compare with the laboratory-induced pain due to its, transient, maximal and experimental nature. Future investigations looking to further investigate the IC pain experience may choose to do this in a different manner. For example, if the aim is to record the normal, everyday occurrence of IC pain, it may be more effective to use a postal survey method and ask participants to complete MPQs for the pain they experience during different activities of daily living.

Overall, these limitations may reduce the power of the initial validation of the mSETT and the external validity of the IC pain description. Nevertheless, the methodological choices that led to these limitations were either made due to feasibility of the project or as a compromise to help achieve other aims of the research.



## 10.5: CHAPTER 10 SUMMARY:

---

This chapter aimed to analyse and compare the pain experiences recorded during the studies described in Chapters 8 and 9. This analysis was completed in an effort to examine the pain experience of IC and compare this experience to that induced by the mSETT. This analysis thus explored the subjective descriptions of IC pain whilst also evaluating the ability of the mSETT to act as a pre-clinical model of IC pain.

The findings of this analysis indicate that IC pain is a multidimensional experience. It is characterised however by certain key adjectives. Sensory-discriminative components focus on adjectives of 'cramping', 'aching' and 'stabbing'; affective-motivational components 'tiring' or 'exhausting' and cognitive-evaluative components 'spreading', 'tight' and 'nagging'. This pain experience is similar to those recorded in other chronic pain syndromes with sensory components reflective of a nociceptive pain experience related to ischaemia (Lang et al 2009).

The pain experience of the mSETT is similar to that of IC although more intense. Similar subclasses of adjective were used to describe mSETT and IC pain. However, the precise adjectives chosen were commonly more intense and reflected those recorded with patients with critical ischaemia. Nevertheless, the mSETT can be seen to induce pain similar in nature to IC and is thus a suitable pre-clinical model. With more investigation and slight modification of experimental parameters, the intensity of pain could be more closely matched.

## CHAPTER 11: AN INVESTIGATION INTO PATIENTS' EXPERIENCES OF USING TENS FOR DAILY LIFE WITH PAD AND IC

---

### 11.1: AIM OF CHAPTER 11:

---

The aims of this thesis are 1) to investigate the subjective description of the multidimensional qualities of ischaemic pain and 2) to investigate the hypoalgesic effects of TENS on lower limb ischaemic pain and walking performance in patients with IC. The first aim has been addressed by the studies described in Chapters 8 and 9 and the analysis described in Chapter 10. The analysis of MPQ descriptions of laboratory and clinical ischaemic pain indicate that it is a unique experience, characterised by certain adjectives. The second aim was also addressed by these studies. TENS was found to increase time to pain threshold, tolerance and endurance in laboratory ischaemic pain and increase walking distance on the treadmill in patients with IC. An important question however, not addressed in any of these studies is: if provided with a TENS machine and training for use at home, would patients with IC use the device and do they feel that it is a useful adjunctive intervention for their disease?

The following chapter will describe a study that was conducted with the aim of beginning to address this question. This study took the form of a pragmatic, qualitative follow-up investigation to the clinical study of TENS described in Chapter 9. First, the methods employed and findings of the study will be discussed (sections 11.2 and 11.3). This will then be put into the context of previous research concerning the lived experience of PAD and IC (section 11.4).

### 11.2: METHOD:

---

#### 11.2.1: Methodological Justification:

---

The aim of this study was to explore the patient experience of using TENS at home for daily life with PAD and IC. As this aim of the study was concerned with individually constructed meanings, a qualitative approach was assumed with the aim of exploring the participants' experiences and generating knowledge surrounding the use of TENS.

There is no distinct definition of qualitative research. The principles are employed in different ways depending on the discipline and concept of interest. In general terms, qualitative research can be described as “an empirical method of investigation aiming to describe perception and experience of the world and its phenomena” (Neergaard et al 2009 p1). Within qualitative research there are three commonly utilised approaches: ethnography (Geertz 2001), grounded theory (Glaser and Strauss 1967) and phenomenology (Sokolowski 2000).

Ethnography is a qualitative research design that focuses on exploring the cultural phenomena in a group of people (Savage 2000). There is no single agreed definition of ethnography although one accepted description is that an ethnographical study is characterised by a mixture of qualitative and quantitative data collection, importantly including participant observation through prolonged fieldwork with associated time and resource implications (Savage 2000). The main limitation of adopting an ethnographic approach is the considerable time and resource implications. To be able to complete the process rigorously, extensive fieldwork is required to enable participant observation, which also has ethical implications (Alcadipani and Hodgson 2009). Ethnography however is especially suited to exploring and developing theory of behaviour in a group of individuals. As the current study aimed to elucidate the participants’ individual experiences of using TENS at home, ethnography was not deemed an appropriate approach.

Grounded theory is concerned with developing theory through systematic collection and analysis of data (Glaser and Strauss 1967; Corbin and Strauss 1990). Characterised by clear methodological choices and specific steps in analysis, grounded theory is a commonly employed methodology in the healthcare literature. Grounded theory therefore describes the general methodology for developing theory that is ‘grounded’ in data that has been systematically collected and analysed (Corbin and Strauss 1990). Criticisms of grounded theory include the ability of the researcher to ‘ignore’ all related theories and preconceptions until later on in the analysis process. This ‘bracketing’ of knowledge is

difficult to achieve (Allan 2003). Nevertheless, as a description of well-developed qualitative research methods there are a number of useful principles that can be employed as elements in non-grounded theory research (Corbin and Strauss 1990). As the current study was not aiming to develop a 'theory' of participant experience of using TENS, grounded theory was not employed.

Distinct from ethnography and grounded theory, phenomenology is a method of study that focuses on the phenomenon, or more specifically, the perception of phenomena by the subjects under examination (Sokolowski 2000). To achieve this perspective, thick description is used to explore how the subject consciously experiences reality. They are encouraged to engage with the world and make sense of it directly and immediately. The ultimate aim of phenomenology is to develop understanding regarding lived experiences by exposing assumptions about the ways of knowing (Starks and Brown Trinidad 2007). There are many benefits of this approach and phenomenology has allowed great development in the understanding of human consciousness and subjectivity (Giorgi 2005). This method could be useful for the current study as it examines the participants' experiences of using TENS for daily life with PAD and IC. However, there are challenges when adopting a phenomenological approach. Due to a strict philosophy and specific approach, qualitative research termed 'phenomenology' often is unable to follow the correct methods of the approach (Giorgi 2006). These difficulties in achieving true phenomenological study are especially true in a healthcare context where research questions do not tend to lend themselves to a purely philosophical approach (Norlyk and Harder 2010). Any variation in method can cast doubt on the findings thus intricate planning and careful analysis is required to ensure success (Caelli 2001; Giorgi 2006).

Due to perceived limitations with these approaches and the difficulties experienced when attempting to employ strict theoretical approaches in a changing healthcare research context, new qualitative methodologies have developed. These include, interpretive phenomenology (Benner 1994), interpretive description (Thorne et al 1997; Thorne 2008) and qualitative description (Sandelowski 2000, 2010). These methodologies are built upon

the foundation of the methodologies mentioned above although they are more practice-focussed and aim to answer specific questions rather than focussing on theorising phenomena (Thorne 2011).

As the aim of the study was to explore the participants' lived experience of using TENS at home for PAD and IC, a phenomenological approach was assumed. The collection and analysis of the data however could also be described as qualitative description as a conscious attempt was made to stay as 'close to the data' as possible and limit the influence of any of the researchers' preconceived perceptions (Sandelowski 2010).

Qualitative description does not possess strict boundaries in terms of methodological choices. Rather it is a series of principles that guide systematic inquiry. The important characteristic of qualitative description is that it is founded in existing knowledge, thoughtful linkages and clinical experience rather than the more classically theory-driven approaches of phenomenology and grounded theory (Sandelowski 2000; Neergaard et al 2009; Sandelowski 2010). A central difference between qualitative description and the other methods mentioned above is the method and aim of the research process. Qualitative description does not aim for thick description (ethnography), theory generation (grounded theory) or interpretive meaning of an experience (phenomenology). Rather the focus of qualitative description is to produce a "rich, straight description of an experience or an event" (Neergaard et al 2009, p 2). This type of analysis fits with the aims of the current study: to explore participants' experiences of using TENS, not to generate theory regarding the use of TENS at home for PAD and IC. Criticisms of qualitative description question whether 'pure description' is possible as there will always be a level of interpretation by the researcher during the analysis. As discussed by Sandelowski (2010), qualitative description does not claim absence of interpretation, just limited interpretation as with any descriptive analysis (Giorgi 1992). Therefore, a phenomenological-based, qualitative description approach was assumed for the current study.

---

### 11.2.2: Design:

---

Ethical approval for the study was obtained from the local National Health Service Research Ethics Committee. The study design was a pragmatic, phenomenological, focus group study. All participants were provided with a TENS machine, training and instructed to use it daily. After one month, all participants were invited to attend a focus group where they discussed their experiences. Prior to, and after the trial one month later, participants were asked to complete four short questionnaires (Figure 11.1).

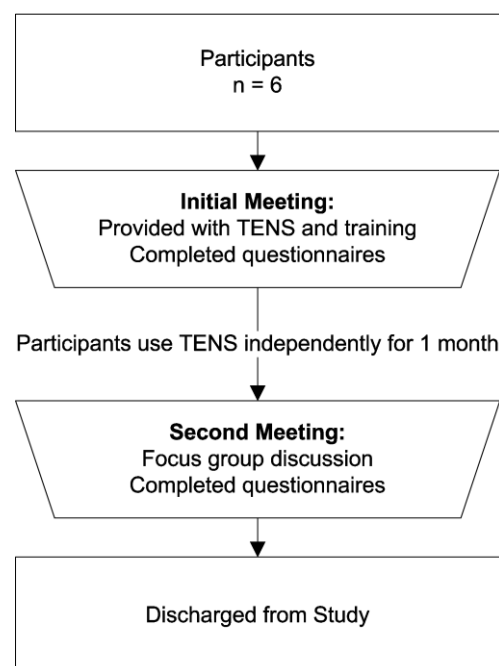


Figure 11.1: Study procedure

---

### 11.2.3: Participants:

---

A sample of 6 patients with stable PAD and IC were recruited from the original study population (Chapter 9). All 36 participants were approached via letter (Appendix 12) and the first 6 to reply were recruited for this study. Each participant received an information sheet and consent form (Appendices 13 and 14). If they were willing to participate in the study, they were asked to return the consent form along with a reply slip (Appendix 15) in a pre-paid envelope.

#### 11.2.3.1: Inclusion and Exclusion Criteria:

---

The inclusion and exclusion criteria used for this phase of the study are the same as that used in the previous clinical study.

##### Inclusion:

- Clinical diagnosis of PAD and stable IC of >3 months duration
- Fontaine stage II
- Resting Ankle Brachial Pressure Index (ABPI) <0.90 in at least one leg
- Walking limited only by claudication
- Independent and safe mobility (no walking aids)
- Cognitively stable and able to follow instruction (MSQ score of 10, MMSE score of 30)
- Proficient in English (able to read and complete the questionnaires)

##### Exclusion:

- <40 years of age
- Planned surgical or endovascular intervention for PAD
- Any leg ulceration
- Any Exercise-limiting co-morbidities e.g. congestive cardiac failure, angina, dyspnoea, MSK or neurological impairment
- Co-morbidities causing pain in the lower limb
- Ataxic gait or history of increased falls (unsafe for treadmill walking)
- MI  $\leq$  6 months ago, Cardiac arrhythmia or Cardiac pacemaker
- Current or previous sensation abnormalities in the lower limbs e.g. severe peripheral neuropathies
- Cognitive deficits
- Epilepsy
- Medical diagnosis or self-reported psychiatric illness
- Previous experience of using TENS

---

#### 11.2.4: Procedure:

---

##### 11.2.4.1: Initial Meeting:

---

Participants attended for an initial meeting, held in a private meeting room within the University campus. During this meeting, their informed consent was obtained, they completed two questionnaires and they were issued with a TENS device and trained in its operation by the primary researcher. They were also issued with step-by-step written instructions (Appendix 16), information, spare batteries and electrodes. The participants were informed that the device was being investigated for its effects on pain and walking performance. Any further questions or queries from the participants were addressed and the day and time for the focus group arranged.

##### 11.2.4.2: Second Meeting:

---

At the end of one calendar month, participants returned to the same room at the university for the second meeting. The primary researcher facilitated a focus group discussion. An independent researcher was present to make notes on interactions and body language. Both researchers were familiar with the focus group topic guide (Figure 11.2). This guide was developed and the focus group carried out in a manner consistent with recommendations by Barbour (2008). The guide was developed by the primary researcher and reviewed by a clinical specialist in PAD who works with patients at the recruitment site and with specialists in focus group research. The primary researcher assumed the role of interview moderator for the focus group.

The participants were introduced to the procedure of the focus group and completed four questionnaires. They were then asked to comment on the statements presented by the interview moderator (see Appendix 17). Discussions were audiotaped and an independent researcher took supplementary notes during the discussions. At the end of the focus group, participants were debriefed and an overview of the discussion presented by the moderator. Participants were invited to comment on the summary and to indicate any discussion points that might have been overlooked or misinterpreted (Galea et al 2008).



### **Focus Group Topic Guide:**

*Start with introducing focus group and purpose of discussions: to elicit participants' experiences of living with PAD and IC and using TENS for walking.*

- Thank you very much for coming along today. Can you please, as an introductory task, tell us your name and something you like to do in your spare time?
- You have all been invited along to this discussion as you have PAD and IC and have been issued with a TENS machine for the past month. I'd like you to speak freely and explain your own opinions and experiences in the discussion.
- I am going to read out a series of statements that will relate to your experiences. I would like you all to respond to these statements, contributing your opinions and sharing your views with each other

*Present these statements, one at a time, to the participants (prompts if required)*

- “Going for a walk is not a problem for me”
  - What factors, if any, affect your decision to go for a walk?
  - How do you feel when you know you have to walk somewhere?
  - Do you ever walk for pleasure/exercise?
- “There is nothing that I can do to about my disease”
  - Have you received/sought any advice?
  - What do you know about the disease?
  - How did you find this out?
  - What treatment options are available?
- “The worst part of the disease is the pain”
  - What frustrates you most about the disease?
  - When you think about your medical problems, what first jumps into your mind?
- “TENS is the perfect treatment for walking in IC”
  - Does TENS make any difference to you?
  - How does it affect your walking?
  - Does its effectiveness wear off?
- “TENS is easy to use for people with PAD and IC”
  - What would you change about it?
  - Would you use it differently?
- “TENS is not for me”
  - What is it about using TENS that you don't like?
  - Do you like the feeling of the stimulation?
  - Are you self-conscious when using TENS?
  - Do you tell people you are using it?
- “TENS reduces the pain experience of IC”
  - What changes, if anything, about the pain you feel in your legs when you use TENS?
  - Does it work in any other way?
- Do you have any other thoughts about TENS and/or walking activity that we may not have discussed already?

Figure 11.2: The focus group Topic Guide employed within this study.

#### 11.2.4.3: Questionnaires:

---

Participants were asked to complete four questionnaires during the study (Appendix 18):

1. International Physical Activity Questionnaire (IPAQ) (Craig et al 2003)
2. Vascular Quality of Life Questionnaire (VASCUQOL) (Morgan et al 2001)
3. Short Form McGill Pain Questionnaire 2 (SF-MPQ-2) (Dworkin et al 2009)
4. Patient Global Impression of Change Scale (PGIC) (Farrar et al 2001)

At the initial meeting participants completed the IPAQ and VASCUQOL with the aim of recording a baseline of function and quality of life. At the second meeting, participants completed the IPAQ and VASCUQOL along with the MPQ-SF-2 and PGIC as a general indication of pain quality/intensity and their impression of the effects of TENS intervention.

#### 11.2.4.4: Analysis:

---

When conducting qualitative research it is important to be explicit regarding the definition of terminology (Braun and Clarke 2006). This is necessary as commonly used terms such as coding, category or theme often have different meanings for different researchers. The meanings of these terms as far as this research is concerned are indicated below.

##### Coding

---

Coding is the process of identifying and labelling a transcript. Coding recognises words, sentences or sections that can be summarised by a short key word or short phrase. For the purposes of the current study, coding was used to identify meaning units.

##### Category

---

During qualitative analysis, categories are used to group and organise the coding of data. Categories are usually formed based on a shared characteristic.

## Theme

---

A theme can be defined as the classification of discrete concepts (Ryan and Bernard 2003). A theme should convey an important and common characteristic within the data and relate to the overall category.

## Sub-Theme

---

As themes are a collection of discrete concepts they often contain a range of sub-themes. Sub-themes can be defined as “themes-within-a-theme” (Braun and Clarke 2006 p92). Especially common in large and complex themes, sub-themes help to provide structure and define the constituent parts of the overall theme.

## Process of Analysis:

---

The discussions were transcribed verbatim, including non-verbal expressions such as silence and laughter. The text was analysed using manifest and latent content analysis (Berg 2009). Manifest content analysis focuses on the explicit words and their denotations whereas latent content analysis concerns the implicit ‘meaning’ and aims to capture the structural meaning of the text (Berg 2009). For the purposes of this study, manifest content analysis was used to describe the experience of living with PAD and IC and practical issues with using TENS. Latent content analysis was used to elucidate the meaning of these experiences and how they relate to general quality of life.

The text was read, and reread independently by the primary researcher (CS) and a second, neutral researcher who was not part of the original research (0-2 months post data collection). Both of the readers identified ‘meaning units’ within the text i.e. words and phrases thought to carry a meaning of importance for the research questions (Wann-Hansson et al 2008; Berg 2009). Similar to the analysis employed by Wann-Hansson et al (2005), each meaning unit was tested and explored using the questions:

1. ‘What is it about?’
2. ‘What does it mean?’
3. ‘What effect does it have?’

These questions allowed the meaning units to be sorted into sub-themes, themes and categories. Initially, meaning units were sorted under the two main categories: 'Living with PAD and IC' and 'TENS for daily life with PAD and IC'. An open-coding technique was employed to identify descriptive sub-themes that were 'grounded' in the data e.g. 'grin and bear it' or 'coping with pain'.

Once completed, the researchers met to discuss the sub-themes identified. Differences in analysis were addressed through discussion and reflection. The main source of discussion related to meaning units that were 'double-coded'. Some meaning units appeared to relate to more than one of the identified sub-themes and discussion was required to come to a decision about which to retain. This discussion was held in the light of the overall analysis to ensure that the meaning units were coded under the sub-theme they best represented. Throughout this process, the focus remained on the manifest content of the meaning units.

When agreement was reached, the researchers sorted the data by sub-theme and discussed their possible latent content. Through these discussions grouping of common sub-themes led to the formation of the themes e.g. 'acceptance, adaptation and control of pain and disease' (See Appendix 19 and Table 11.3).

This process included constant reflection, discussion and re-evaluation by both researchers (2-3 months post data collection). All participants were sent an abridged report that included brief descriptions and examples of the themes for 'member validation' (3-4 months post data collection). All participants were in agreement that these themes accurately described the focus group discussions.

### 11.3: FINDINGS:

---

#### 11.3.1: Participants:

---

Five participants (4 men) attended the focus group. The sixth participant withdrew due to illness unrelated to the study. Participant demographic data is detailed in Table 11.1.

All participants were aged 55 or over, (mean age = 70.4, range = 55-82 years). The length of time from original diagnosis ranged from 6 months to 6 years. All participants had ilio-femoral disease and ABPIs ranging from 0.41 to 0.81. The mean values were similar to those of all the participants in the main study (Table 11.1). In general, participants in this follow-up study had more severe disease (lower ABPI), shorter walking distances and lower WIQ scores. Participant 1's ICD, FCD and ACD were considerably greater than the other participants, skewing the distribution (shown by the difference between the mean and median). Participant 4's PCS score was greater than the other participants within this study and also greater than the mean for all the clinical study participants. This indicates that they have greater catastrophic beliefs related to pain. Participant 1 also reported the highest level of activity in the IPAQ and greatest quality of life as measured by the VASCUQOL, linking with their greater walking distances. The oldest participant (No. 2) had the lowest reported IPAQ and VASCUQOL scores along with the lowest ABPI although their ICD, FCD and ACD was comparable to the other participants (Table 11.1).

All participants had coexisting illnesses other than PAD with the most common being hypertension and hypercholesterolemia (all participants). No participant had diabetes mellitus.

**Tables 11.1 and 11.2 Key:**

ABPI	Ankle Brachial Pressure Index
ICD	Initial Claudication Distance (m)
FCD	Functional Claudication Distance (m)
ACD	Absolute Claudication Distance (m)
WIQ	Walking Impairment Questionnaire (%) (Greater score = less impairment)
PSEQ	Pain Self-Efficacy Questionnaire (Greater score = greater pain self-efficacy)
PCS	Pain Catastrophising Scale (Greater score = greater catastrophising beliefs)
TSK	Tampa Scale of Kinesiophobia (Greater score = greater pain-related fear)
IPAQ	International Physical Activity Questionnaire (1-3; 1=Inactive, 2=Minimally Active, 3=HEPA Active)
VASCUQOL	Vascular Quality of Life Questionnaire (0-6; greater = greater quality of life)
SF-MPQ2	Short Form McGill Pain Questionnaire 2 (0-10; 0 = no pain, 10 = worst possible pain)
PGIC	Patient Global Impression of Change Scale (Activity Limitation = 1-7; >4 = positive change; TENS = 0-10; 5 = no change, lower = more improvement)

Table 11.1: Participant demographic data at baseline. Coloured shading represents comparison between participants with darker shades of green indicating 'favourable' properties.

Participant	Age (years)	Disease Duration (months)	ABPI	ICD	FCD	ACD	WIQ	PSEQ	PCS	TSK	IPAQ	VASCUQOL
1	68	24	0.57	270	931	1200	49	56	5	33	3	4.8
2	82	24	0.41	99	160	181	13	28	19	39	1	3.4
3	71	6	0.61	25	94	117	42	38	6	40	3	4.3
4	76	72	0.51	43	87	135	32	37	5	30	1	4.1
5	55	36	0.81	48	135	165	45	48	37	39	3	4.3
<b>Mean</b>	70	32	0.58	<b>97</b>	<b>281</b>	<b>360</b>	36	41	<b>14</b>	36	2	4.2
<b>Median</b>	71	24	0.57	<b>48</b>	<b>135</b>	<b>165</b>	42	38	<b>6</b>	39	3	4.3
<b>Chapter 9 Mean</b>	70	NA	0.63	86	202	259	48	40	12	38	NA	NA

The mean and median values are reported as an aid for interpreting the results of the study and for comparing with the mean for the overall study population described in Chapter 9 (also included). Highlighted in **bold** and in outline are the variables with a large change between mean and median values suggesting the presence of an outlier.

Table 11.2: Participant data at baseline and follow-up (post TENS). Coloured shading represents comparison between participants as well as pre and post TENS.

Participant	IPAQ		VASCUQOL		SF-MPQ2	PGIC Scale	
	Baseline	Follow-up	Baseline	Follow-up		Activity Limitation	TENS
1	3	3	4.8	4.8	0.7	6	1
2	1	2	3.4	3.9	1.1	2	5
3	3	3	4.3	6.1	0.5	4	2
4	1	1	4.1	4.6	0.2	2	5
5	3	2	4.3	4.8	0.8	3	3

---

### 11.3.2: Methodological Considerations:

---

The aim of the current study was to conduct a primary evaluation of use of TENS for daily life in a group of patients with PAD and IC. To achieve this aim, focus group discussions and content analysis were selected as the methodology of choice.

To date, all qualitative studies examining the experience of living with PAD have used semi-structured, individual interviews to gather the data. The current study employed a focus group methodology with the aim of being more natural, encouraging participant interaction and allowing contrasting opinions to be easily explored (Kitzinger 1994; Wilkinson 1998; Berg 2009).

Manifest and latent content analysis (Berg 2009) were employed in an attempt to describe all aspects of 'the experience of living with PAD and IC' and 'using TENS at home for daily life with PAD and IC'. Manifest content analysis was used to elicit the descriptive and functional meanings of the discussions while latent content analysis aims to focus on the underlying meaning of the discussions (Berg 2009). There are multiple meanings present in data and there is no right meaning, only the most accurate meaning from a particular perspective (Downe-Wamboldt 1992). This type of analysis seemed to encompass all the possible meanings and provide the richest interpretation of the data.

Lincon and Guba (1985) proposed four criteria that should be considered when evaluating interpretive analysis to improve trustworthiness: 1) credibility, 2) transferability, 3) dependability and 4) conformability. These criteria can be viewed as corresponding to: 1) internal validity; 2) external validity/ generalisability; 3) reliability and 4) objectivity in the positivist research paradigm (Shenton 2004).

The issue of credibility was addressed in this study by examining and employing similar methods to the previous literature in the area. Also, at the end of the data collection and analysis stages, member validation was used to ensure it was a true representation of the discussions.



Due to the nature of qualitative research, the findings are context-dependent and the issue of transferability is thus debated. Nevertheless, to enable the clearest extrapolation of the results, participant demographic data was collected and is presented here along with other information to describe the specific context and aid in the generalisability of the findings.

It is argued that credibility somewhat ensures dependability in qualitative research (Lincon and Guba 1985). Shenton (2004) indicates that further steps can be taken to increase the repeatability of the study and thus the intrinsic dependability. Therefore, with this in mind, this report includes detailed descriptions of the research design, data collection and data analysis.

As the primary researcher was involved in the original study and immersed in the project, there is a considerable risk to the conformability of the research. To combat these issues, two main methodological issues were addressed. Firstly, to provide a clear 'audit trail' the analysis tables including verbatim quotations are included in the appendices (Appendix 19). This allows independent examination of the analytical steps. In addition, a second researcher who was naïve to the project analysed the transcripts independently and both researchers reviewed all analytical decisions.

---

### 11.3.3: Themes:

---

Before examining the experience of using TENS, it is important to establish the context in which it was being used. To this end, the experiences of this specific group of patients of living with PAD and IC will first be discussed followed by that of using TENS.

The experience of living with PAD and IC was found to be characterised by feelings of frustration linked to a number of aspects of the disease. This was interpreted through five themes (Table 11.3). These themes will be explored alongside verbatim quotations from the focus group discussions. The experience of using TENS in daily life was characterised by a

combination of benefit and disappointment. These themes will be explored in turn with specific reference to the experience of living with PAD and IC.

Table 11.3: Summary of interpretation of patients' experiences of living with PAD and IC and using TENS for daily life in patients with PAD and IC

<b>Category: Living with PAD and IC</b>		<b>Category: TENS for daily life with PAD and IC</b>	
<b>Themes:</b>	<b>Sub-themes:</b>	<b>Themes:</b>	<b>Sub-themes:</b>
Frustration	Transient pain 'Grin and bear it' Social limitation	Pain	Sensation Walking ability
Pain	Fear Disease perception Physical limitation	Control	Benefit
Limited physical and social functioning	Walking ability Transient pain Social activities	Expectations	Masking the pain Beliefs
Acceptance, adaptation and control of the pain and disease	Acceptance Control Coping Physical Limitation Walking ability Risks and benefit Treatment options	Usability	Technical specifications Sensations
Knowledge and understanding	Education Others understanding Attitudes and beliefs Benefits of walking Expectations	Physical and social functioning	Social activities Walking ability

#### 11.3.3.1: The experience of living with PAD and IC:

##### Frustration:

The main emotion interpreted from the participants' discussions was frustration. The frustration was related to the transient and mild nature of the pain experience. They felt that the pain is not severe. However it is significantly disabling. It seemed to be this contrast

that frustrated the participants. This indicates possibly that if the pain was more intense their limited mobility would be validated somewhat? This lack of intensity also seemed to be related to the transient nature of the pain i.e. the pain disappears as soon as they stop walking; therefore the pain is not perceived as being particularly intense.

*[P5] when it goes away you are like, well fine but when you go away again back it comes again so you stop again. That is, it is more frustrating than anything*

*[P4] that's the worst part of this bloody pain, it's the frustration of the pain ... it's not going to kill you but it is really debilitating ... the thing is its sore but once you stop, it's gone ... that's what puzzles me all the time ... you think, oh god and you sit down and all of a sudden, bang and it's not there*

*[P4] But as I say they say 'grin and bear it' but this has been going on for years and years for me, it's like having a leg off- grin and bear it so you just, what can you do?*

*[P5] there is only one thing that takes the pain away and that is when you sit down ... that takes the pain away ... and the frustrating thing is you only have to sit for half a minute if at that and it is away. Then you walk again and it comes back*

Similar to when participants discussed their pain, feelings of frustration were key components when discussing any limitations in lifestyle. The feelings of frustration expressed by the participants were primarily related to social situations that they are not able to participate in fully as before.

*[P5]: the same as when you are walking to the football with them we have got a good bit, maybe, hmm I don't know, 20 minute walk from the ground to the bus well, I'm like, miles behind them cause I cannae keep up with them ken what I mean. And even a lot of them are a lot older than me and they can ..... and you say to yourself 'how?' it's the most annoying thing but once I stop like, I just need a minute and away I go again and its fine for maybe another couple of minutes then I have to stop again. That's the most frustrating thing about it- you have got to stop.*

Along with frustration related to attempted participation there was also frustration related to an inability to participate. Simple tasks and Activities of Daily Living (ADL) are not possible and this lack of ability to fulfil their perceived role is reported as frustration.

*[P4] and it is that bloody frustration and then you think you will not bother coming the next time, I am just stuck indoors now and I can't even go out in the garden to help the*

*missus and she's like get yourself indoors, it's that frustrating, it's not the pain. It's just up here (points to head) it's not the pain*

Even when they do participate, it is not necessarily personal frustration about their ability to complete the task, but that they feel as though they are an inconvenience to others that frustrates them more.

*[P4] you are a nuisance to them .... cause you are taking so long ... it is, that's the worst part about this pain, it's the frustration*

A few participants expressed feelings of frustration related to the lack of options and the fact that healthcare practitioners just tell them that they need to put up with it.

*[P4] it is, they keep saying 'grin and bear it' and that's all I have been doing for years and years now.....*

*[P5] yeah, me too- the very same; I'm just like, it will be 5 year, maybe 6 years I have had it and you just have to put up with it.*

As well as their own understanding, the patients report feelings of frustration related to others' understanding of their condition and specifically the pain.

*[P4] the thing is you bleeding, you just think you can go on a bit more, a bit more and then you say no I can't and you stop and the pain is gone ..... it's funny, you know you can't explain it to people what it is like unless they have had it you know like you*

*[P5] that's what I'm saying, other people dinnae understand what the pain that you go through, ken what I mean?*

#### Pain:

The discussions were interpreted to have a focus on the pain, a difficult convergence of a transient, yet chronic experience. Participants describe a classically intermittent experience that they were able to control to an extent although they also reported frustration regarding the chronicity of the prolonged experience with no perceivable endpoint.

Pain was interpreted as the defining factor of the disease rather than the general systemic arterial disease that they are suffering. This is understandable as the pain is the daily,

debilitating symptom. Nevertheless, it is interesting that none of the participants discussed the general disease process and its implications. This could have been because they were attending this study that focussed on reducing the pain in their legs with TENS and therefore may have thought the focus of interest was pain. However, it could be a more general indication related to the way in which PAD and IC are managed and the education and advice these patients have received.

*[Moderator: I want you to just think about your health in general, what first jumps into your mind, what's the first thing you think about?]*

*[P2] the pain in my leg.*

*[P5] the leg, exactly.*

*[P2] it stops you doing everything really.*

*[P5] that's the only thing really, thing that bothers me, is the legs.*

*[General agreement]*

Most of the participants had been advised to use paracetamol as pain relief. Often the reason provided for this was that this is the strongest form of analgesia they can take due to interactions with their other medications. The participants were laughing at this as they feel that paracetamol is inadequate as pain relief. They feel they need stronger painkillers and that, if provided, they would help.

*[P3] Paracetamol is what they say [General laughter]*

*[P3] I might as well have a couple of sweeties ..... I can't have anything stronger than paracetamol because of the other things I am on but I might as well have a sweetie for all the good it does, it doesn't make any difference*

This is a passive solution and indicates the biomedical-based beliefs of some of the participants. They feel as though they need an 'intervention' to 'fix' their pain and they have no control over their situation.

When asked what they feel restricts their participation in normal activities, the participants report it is the pain rather than any limitation in ability to mobilise. Of course, this could be argued to be one and the same thing. This focus on the pain however, indicates that the patients perceive that it is the pain that limits their quality of life and participation in normal

Activities of Daily Living (ADLs), rather than the decreased mobility. In terms of interventions to address these issues, strategies that reduce the impact of pain may be most effective.

#### Limited Physical and Social Functioning:

Another theme that was interpreted from the discussions relating to pain was that of walking ability. Participants discussed this as an important factor of the disease. In essence, it seemed to be the fact that their pain and disability was outwardly obvious and therefore, embarrassing to them. This was especially evident in social situations when their impairment affected their participation.

*[P5] see the likes of when you have to carry on you try to keep up with them (the football crowd) ..... you start walking like all kind of funny like you have done the toilet in your pants, but you do because my brother has said to me many times,*

The environment was reported as an important factor that determined physical activity in this group of patients. This is another important factor to be cognisant of when planning general lifestyle interventions for IC.

*[P1] well em, not particularly. I can walk on golf courses if it is nice and flat and it is soft, going for a walk on hard roads is a problem for me and climbing up hills*

Along with not being able to complete normal household chores or social activities, the disease seems to affect participants Quality of Life (QoL) in other ways. Walking a dog would be greatly helpful for this patient population in terms of exercise and general cardiovascular health. However, because of the experience of pain and a lack of adequate counselling and support, they are dissuaded.

*[P2] I couldn't even contemplate having a dog now because I wouldn't be able to walk it*

This feeling of frustration related to being an inconvenience to their friends and family was common among the participants and resulted in non-participation in activities.

*[P2] to come and do something, the first thing you think of is how much walking is involved ..... and will I just be a damned nuisance if I go because I will be trailing back and behind the others .... you know? And you just don't go*

This non-participation due to the pain was true also for hobbies although there seemed to be a greater attempt to adapt and continue participation in some activities. This is very positive and important for maintaining activity and general cardiovascular health. Not all participants had managed to continue with their hobbies and it would be important to ascertain what contributed to this participant's decision process and try to instil this in others with IC.

*[P4] it's the same on the golf course, I've had to give up golf because you cannae, you cannae get, you pay to play 18 holes and you cannae get round, you get round about 8 and that's it, and your mates are saying 'come on' and you say I wish I could come on but that's it and so I've stopped playing the golf and I've taken the bowling up and that's helped me a hell of a lot, the bowling, and that 3 days a week for about 2 hours and I really look forward to that and funny enough when you are on there bowling, from the car to the bowling green your pain is there but once you get on the bowling green it is gone*

#### Acceptance, adaptation and control of the pain and disease:

---

The text exposed a degree of acceptance by the participants related to the pain they experience.

*[P5] you just have to put up with it because you will get it, you will get the pain every day so you just have to get used to it, put up with it*

This could be interpreted as positive acceptance of the pain. However, the last four words of the sentence ('put up with it') seem to convey negative connotations. A lack of acceptance may suggest that the disease is seen as finite i.e. that they will not always experience the pain but it is something they just have to put up with for now.

The participants' general approach to the disease and pain was that they were stuck with it and nothing was going to change, or there is nothing they can do to change it. This also relates to participating in activities where, in some cases, they feel they just have to get on

with it because they want to do the activity and that means more to them than avoiding the pain.

*[P5] because I don't want to sit in that house, ken what I mean? ..... no way, so you just have to put up with it.*

*[P4] yep, the world's always saying to me 'grin and bear it'*

*[P2] 'grin and bear it'.*

*[P5] exactly.*

*[P4] and that's been happening for 6 years, 'grin and bear it'*

Participants all displayed a clear understanding of the control they have over the pain. They know it will go away if they stop walking although this is contrasted with the distinct feeling of lack of control related to the long-term course of the disease and prognosis for the pain.

*[P3] that's your tablet isn't it? That's your simple cure- just stop walking and there is no pain*

*[P5] you have got to stop, ..... your mind is saying to you, 'stop and it will go away if you stop' ..... that's right, it does go away yeah so you say to yourself, "what's the point?"*

Participants seemed to feel that it was important to mention and discuss the fact that they hadn't changed because of the disease. This could indicate that they don't feel that the disease has affected them too much but this was not borne out in the rest of the discussions. It might be that the patients are motivated to present a strong outward image in front of their peers. However, it could be that they are employing denial as a coping strategy i.e. they are not ready to accept the degree to which they are limited by the disease.

*[P5] I've not changed, you just get on with it and that's it. You get used to it ken*

The understanding that walking can help the condition seemed to be empowering for the participants. They are aware that their condition is progressive and in this participant's case, inoperable, so to have something they can do to reduce the effect of the disease or slow its progression affords them a sense of control.



*[P1] I don't think there is very much I can do about it .... well, what they told me was my problem is inoperable and em, the best thing I can do is walk as much as possible*

*[P3] if it is going to stop it getting worse, that's what I am doing, I will keep doing it. Obviously, you would like a cure for it but it's not going to happen overnight is it?*

*[P1] because the chances are the more you walk the blood vessels sometimes kick into play ..... that's what I have been told. And I think that my playing golf bears that out*

Nevertheless, others with less apparent knowledge and understanding feel as though there is nothing they can do about the condition. This lack of perceived control seems to lead them towards passive coping where the medical staff have the power and will eventually find a 'cure'. This approach at face value may indicate a perceived lack of control but it may just be the way they have chosen to cope i.e. they feel they are powerless and thus attribute all the power to healthcare staff rather than being frustrated by trying to control something that they are unable to.

*[P3] if what you are doing is going to help in the future. I can't see you getting a pill that will cure it, obviously it is going to be something surgical I would imagine*

*[P4] there is nothing you can do to change it.*

*[P5] yeah, well that's what I think, that's my theory as well*

*[P4] You look back and the things I have got to take I think I am taking these because the doctor says to take them but is it making any difference? Say if I was to stop them, would it make it worse?*

The treatment options or the methods with which they can control the disease contribute to a sense of 'grin and bear it'. Due to the perceived lack of effect of their options they feel as though they just need to get on with it, and/or accept that they will experience the pain.

Participants discussed common strategies they employ to cope with the pain. They reported that when walking, they're constantly evaluating where the next place is that they can get a seat and rest. It was important to note that they all reported making an effort to hide the fact that they needed a rest. They described going into shops, stopping to look in shop

windows, stopping to cross the road or pretending that they were waiting for a bus at a bus stop. This indicates an embarrassment or just motivation to hide their limited walking ability from strangers.

*[P2] but even before it is sore I think if you are walking you are very conscious of knowing, now I can get a seat just along there or there or I have seen me go into a shoe shop because they have the bits you can sit to try on shoes, I'm no trying on shoes, I just need a seat*

Some participants displayed a strong sense of control and seem to be coping well with the disease. This involved continuing with hobbies and general daily activities despite the pain.

*[P1] one of them said to me, 'I don't know how you can play golf' but you have just got to, if you want to get on with your life you just have to do these things*

This statement can be interpreted as demonstrating a greater level of acceptance of the disease and lifestyle limitation. This acceptance seems to have led to an increased ability to cope with the disease and a willingness to not allow it to limit their lifestyle. Other participants also displayed similar behaviour/ beliefs:

*[P2] when I am doing the ironing and things like that when you are standing you know for a while, and you have got to, you know the washing and ironing is done in small lots so you are not faced with a huge pile and standing for ages and I certainly can't do any gardening, I've had a gardener for quite some time but I couldn't do it*

By changing the way they approached their tasks they are able to cope with the disease and continue to achieve a level of independence.

Overall, the participants most commonly referred to the general coping strategy of just getting on with life. As they feel there is nothing much they can do, or they are doing all they can, they have to just 'grin and bear it'.

*[P3] and they have tried that treadmill with putting all the things on you and that and the lad explained at the time, it's not going to cure you, we are researching it now to see what it is, and until you find out what is causing it but they already told me it's the narrowing of the arteries that's causing it and basically the smoking is causing that. So*

*there is not really a cure for it is there? Unless they take an artery out and replace it and I don't see that happening. I mean and you get to our age, well not P5 but myself like, is it worth the while? Just put up with the pain I certainly wouldn't rush along for it (surgery).*

*[P5] no way, you just put up with it*

With appropriate education and management of expectations, it may be possible to affect and improve behaviour change and compliance with management strategies. This participant, when discussing taking medications displays knowledge and a good understanding of the reasons for taking them and therefore appears to have no problem with it.

*[P3] I have to take one too but it's a preventative measure*

Contrast this with another participant who does not appear to have sufficient knowledge to understand and accept the management strategies. This is important when planning any intervention or management strategy: it must be accompanied by comprehensive educational input to help enhance patient understanding and engagement.

*[P4] You look back and the things I have got to take I think I am taking these because the doctor says to take them but is it making any difference? Say if I was to stop them, would it make it worse?*

### Knowledge and Understanding:

---

Another common aspect amongst the participants was a lack of knowledge regarding the pain experienced. The participants indicated that the mechanisms behind the pain had not been explained fully to them and they had inferred this as healthcare staff not really knowing what is happening. It is important to note that they did not mention seeking this information independently from other sources. A lack of knowledge in the mechanisms of pain has been shown to result in pain-associated fear and avoidance behaviours (Leeuw et al 2007). As the participants see the pain as being from an unknown origin, they are unsure if it is damaging and therefore fear it and avoid activities that cause it.

*[P4] it's like when you say, you're walking and when you stop and you sit down for two minutes and it gone and you think, that's fine, and you get up again and it starts again. That's what nobody has ever said to me, this is what's happening with this disease, because it is a disease. Well you say it is there one minute and it is gone the next, you get up again and its come again, so but they have never explained to me what it is*

*[P4] if they could explain to you what is causing the pain and if they say look, we can't give you anything, well they can't give you anything to get rid of the pain, maybe it helps ease the pain but you can't get rid of it. If they could explain to you what's happening and you could say oh, fair enough then*

In addition, even when the education is appropriate and relevant, it appears that patients do not always follow it.

*[P5] and it's alright for the doctor to say 'lose weight, that will help' but I'm not a big eater anyway so my biggest problem is cheese but I'm no gonna want to stop a things that I love just because the pain because how should I? I like to go for a pint at the weekend with the boys, I'm no gonna stop it ..... because I don't want to sit in that house, ken what I mean?*

The participants demonstrated a general lack of knowledge and understanding of the disease process in general. This uncertainty is not helpful, as patients do not know what they could do to affect their prognosis. The general assumption from the participants and therefore their approach to the disease is one which interprets it as an 'acute' condition i.e. they feel this is an inconvenience but eventually it will be 'cured'. This is an incorrect perception as PAD is merely an initial indication of systemic arterial disease that commonly progresses to myocardial infarction or cerebrovascular accident (White and Gray 2007). It is therefore essential that patients with PAD accept this truth and work to modify their cardiovascular risk factors to reduce the chances of further cardiovascular complications (Milani and Lavie 2007).

The participants seemed to have some understanding of this. However, they were not sure or hadn't been reassured that what they were thinking was correct. With this uncertainty and focus on the present symptoms, the general disease process seems to be forgotten.

*[P3] I have only got it in one leg but I presume if I hadn't taken the medication it would have spread to the other leg?*

*[P4] it is my right leg that bothers me too. If I hadn't have stopped the smoking, would it have got worse?*

*[P5] that's what he said to me, the only option is surgical, well that was like 2 years ago and I don't know if anything has changed now but that was the only thing he said to me would help was that thing like you said ..... the stent or taking another bit out of my leg and putting it in but he said that is the last option*

The participants articulated pain-related fear. This was expressed as a concern regarding the possibility of causing damage by walking in pain.

*[P3] you know it is going to get worse ..... it would be interesting to try to go further just to see what damage you would do but then it is too late by then*

As mentioned above, these beliefs are a direct consequence of patients' knowledge and understanding of the disease. The beliefs expressed during the focus group discussions reflected a sense of fear of pain/ (re) injury.

*[P5] the pain is telling you to stop*

*[P3] it's not permanent damage, you are not doing it permanent damage because eventually you will stop but if you pushed how far, you have done the treadmill you stop there because you are frightened to go a bit further because you don't know what you are doing to yourself*

The participants reported feelings of frustration relating to other people's understanding of their condition. The thing they felt was least understood was the transient nature of the pain.

*[P4] the thing is you bleeding, you just think you can go on a bit more, a bit more and then you say no I can't and you stop and the pain is gone .... It's funny, you know you can't explain it to people what it is like unless they have had it, you know like you*

One participant suggests that the surgeon doesn't actually know what is happening with their disease and therefore doesn't know how to fix it. This could imply a number of different things: 1) that this patients feels that they could be and they need to be 'fixed'; 2)

they have either had a conversation with their doctor who has given them poor advice/ education or they have chosen to interpret advice in this way; 3) they don't understand what is happening in their disease and they truly believe nobody else does, therefore they think it might be all in their head. Either way, the resultant feeling is of helplessness i.e. they can't do anything about it so they have to 'grin and bear it'.

*[P4] you know you think what the hell is the matter because once you stop as you said, once you stop the pain is gone ..... that's what puzzling me all these years and it has been going on almost 10 years now and I keep saying to the surgeon and all that and they said we could tell you what the problem is and we could fix it but we don't know what the problem is so all this is probably helping. But it is frustrating the problem you know is just in here (points to head) you just have to grin and bear it*

When presented with the option of surgery that might reduce their pain and increase their function, one participant refused due to the risk of amputation. This indicates that although they report great frustration related to their pain and disability, this is not severe enough to warrant risking amputation. It could be interpreted that they feel they are able to 'grin and bear it' at the moment so they do not need surgery.

*[P4] as soon as they say you could lose your leg that's me, forget about it, grin and bear it*

With appropriate education and advice, participants demonstrated good coping strategies and behaviour change. When instructed to walk as much as possible along with the knowledge that it might help with the disease, one participant demonstrated clear understanding of the benefits of walking. This indicates that with limited ways in which they can exert control of the disease, appropriate information and understanding of ways in which they can have an effect on their condition and disability have an impact.

*[P1] if I'm told by my doctors anyway without the TENS machine that the more I walk, the better chance I have of my pain maybe dissipating a bit*

#### 11.3.3.2: TENS for daily life with PAD and IC:

---

##### Pain:

---

When using TENS during hobbies and ADLs, participants reported a positive effect. One participant reported that they experienced less pain than normal.

*[P1] a golf course that is quite difficult to walk and I used it and I did have some pain but certainly nothing like what I would have expected to experience.*

The pain reduction reported when using TENS appears to reflect Gate Control mechanisms of analgesia (Melzack and Wall 1965). The TENS employed seemed to work immediately to delay the perception of pain and continue through the experience, reducing the overall intensity.

*[P3] yeah, it sort of numbed the pain, more concentrated, you know instead. The tingling takes it away right away, the initial pain. It was definitely as I say, it has got potential; it is working on the right lines, it's not taking the pain away, just covering it*

##### Control:

---

One of the participants found that TENS helped them so much that they have ordered some more equipment for the TENS machine with a view to purchasing their own. This indicates that TENS helped to foster a sense of control over the pain for this participant and they feel they would like to continue using it.

*[P1] I will tell you how much I found how good, I have already been out and ordered, not that I have used them but I have ordered myself some new pads*

##### Expectations:

---

Another participant didn't think that the TENS machine was useful for them. They reported that they still experienced pain and therefore they think TENS doesn't work. This indicates that this participant's expectations were maybe not properly managed i.e. they thought TENS was going to take away the pain altogether rather than just reduce it.

*[P5] I would say it is easy to use but I don't think it is any good for the disease, well that's just my personal opinion, it didn't do me any good. Well the pain was still there when I was using it*

When discussing the numbing nature of TENS together, it was reported to be positive as less pain was experienced. Nevertheless, despite this discussion some participants were not satisfied suggesting that they were expecting a greater degree of pain reduction.

*[P5] I still definitely got the pain with it when I did use it, did you P3?*

*[P3] oh aye. Aye. I still had it but it was a different form of pain*

*[P5] right*

*[P3] it was sort of numbing, not so sore but it was still there*

*[P2] I didn't feel that this sort of alleviated the pain at all, I was aware of the pulsing as you are saying but to me it wasn't making things any better*

In subsequent conversation, the participant reporting a positive experience of TENS here explains that they had prior experience of TENS. This prior knowledge may have had an influence on their expectations of TENS and thus partially explain their positive reaction.

*[P3] my friend, she bought one, they told her it was a frozen shoulder, she bought one out of the chemist and was using it for about three weeks and she said, perfect, it worked perfect for her. She saw that one likes and the one she got was a lot smaller and she used it for 15 minutes in the morning and 15 minutes at night, shoulder is gone. She has had these injections and that and they didn't do anything for her, so I mean, it must be good isn't it?*

Another participant who reported a positive experience of using TENS also had a similar experience of TENS. They seem to display clear expectations of the effect of TENS. Even though they think this person had a different type of machine, they realise it works in a similar way and therefore any effects it might have had are attributed to TENS.

*[P1] I met a friend, a girl on the golf course and she, somebody had told me she had a TENS machine and I spoke to her and she has got some Japanese, I can't remember what it is called but she found it on the internet and she must be the same sort of thing as the Japanese one, probably a wee bit more sophisticated than the TENS machine because I think she said she paid £70 for it but it has obviously got pads and she uses it for her back and she has found it good*



### Usability:

---

When discussing how easy the TENS units were to use, participants reported little difficulties. One common issue were the wires leading to the electrodes. They suggested a wireless system, or one that they could just attach to their leg rather than their belt would be an improvement.

*[P1] I don't think there is any way that I could think to be improved just the fact that if it is on your legs, you have got to put the wires up through your trousers and then gets onto your belt*

They also reported slight embarrassment when other people observed the unit attached to their belt. Nevertheless, this didn't affect them too much as the pain is such that they are happy to endure slight embarrassment to achieve some relief.

*[P3] even adults were querying what it was. I am willing to try anything  
[P2] that's true, I'd try anything as well whatever might work*

The way the participants reported using TENS varied through the group. In general, they put it on when they knew they were going to be walking for a prolonged period of time. This was explained either as TENS was not needed for shorter journeys, or that it was too much hassle to put it on and off all the time. This is an important factor to consider when prescribing TENS for IC. Also, the device could be modified so that it is easier to put on/ take off which may help to increase the 'usability' of the device.

*[P1] it means I could walk further if I wanted to. The times I have used it..... I use it now only if I am going to be playing 18 holes of golf, I wouldn't put it on if I had to walk down the street to pick something up at the shop it is quite difficult with me it is on a slight hill when I am walking home I feel a slight pain but I wouldn't put the TENS machine on to do that*

More continuous use was reported in other participants. This seems to be more efficient. However, there are possible caveats. As they are using the pads and device for prolonged periods it would be important to constantly monitor the skin for any breakdown or adverse

reaction to TENS. These complications however, were not reported by any of the participants

*[P3] every day, maybe not so much at the weekends but during the week and I didn't put it on today because I was coming here. I would put it on in the morning and take it off at night and when I needed it I switched it on*

Use of TENS was not simple for all participants. This is a common issue amongst new users of TENS. For future studies and clinical utilisation of TENS, the ease of use should be more thoroughly addressed.

*[P1] is it easy to use? I would say for the majority of people, yes but I am one of these technophobe when it comes to any I find anything like that difficult but that is not to say it, that is only because of me, I think most folk would find it quite simple*

Another factor that affects the usability of the device is the feeling of the stimulation. One participant in the study reported this. They had a bad experience in the training session where they turned the intensity up too far so that it was unpleasant for a short while and this seems to have affected their use of the device, as they did not want to experience this again.

*[P5] the thing about it for me was the tingling in my legs with it. I can't bear it  
[P4] oh I didn't mind that, I enjoyed that, the tingling in your legs, aye it helped*

The participants in the study used TENS in different ways. They were not instructed to do anything in particular, as one of the objectives of this evaluation was to ascertain how they might use TENS independently. In general, most of the participants used the device when they knew they were going to be walking for a prolonged period. Half of the participants kept the device on all day and just turned it on whenever it was needed.

*[P2] yes, I put it on in the morning and had it on all day  
[P4] I used it three times a week for 3 hours up and down between the bowling green  
[P5] no for me, I used it once a week because that's the only time I go walking*

### Physical and Social Functioning:

---

Overall, TENS helps to increase walking ability and this has a direct impact on the psychological wellbeing of the participants. This participant reported being able to walk further with the TENS. However, it was the fact that they didn't experience the embarrassment of needing to stop and 'shake their leg' that they focussed on primarily.

*[P1] if I didn't have the TENS and this particular course I'm thinking, I could never get round that course without stopping and having to shake my leg and wait a minute which becomes quite embarrassing when you are playing with someone and you are holding them up*

The participants walked further and experienced less pain while doing so. They seem to be able to push themselves further so they are walking with ischaemia, rather than up to the point of ischaemia.

*[P3] it numbed the pain, you maybe walked a wee bit further. I did notice a couple of times my foot went numb when I had the machine on. Well that has happened before without the machine but it seemed to come on a bit earlier*

Nevertheless, there remained an indication that even though they could walk further, they might not want to. Further investigation is required to examine the determinants of walking in this group of patients although from the discussions observed in this study it could be suggested that a lack of knowledge and understanding of the disease process is a contributing factor.

*[P1] it means I could walk further if I wanted to.*

When using TENS for social activities and hobbies the participants found that it helped them walk further and participate more effectively. They didn't report that it took the pain away completely but it allowed them to walk further and cope with the pain better than without TENS.

*[P1] I find I could get round when I am using it now this is a golf course that is quite difficult to walk and I used it and I did have some pain but certainly nothing like what I would have expected to experience. So to answer your question I would say that the*

*TENS machine definitely lessens the pain whether I could, I can't definitively say that it totally takes the pain away.*

---

#### 11.3.4: Summary:

---

The experience of living with PAD and IC was found to be characterised by feelings of frustration related to pain, decreased walking ability, decreased quality of life and knowledge and understanding of the disease. Other common themes related to coping and 'living with the disease' were identified through participant discussions.

Issues identified in terms of management were a lack of education about the disease process, possible self-management strategies and mechanisms of pain. Future studies should examine the effects of implementing a structured educational and counselling programme for patients with PAD and IC. This may help address many of the aspects discussed including fear of pain, acceptance and adaptation to a chronic condition, increase feeling of control and thus develop positive coping strategies, encourage self-management strategies including walking and maintenance of hobbies, develop understanding of treatment options and expectations of their prognosis. This should also include family and friends to help reduce the feelings of frustration related to the perceived lack of understanding by significant others.

The experience of using TENS at home for PAD and IC was interpreted as being one characterised by general benefit but also unrefined. Participants reported decreases in pain and increases in walking ability leading to increased participation and decreased feelings of helplessness. However, these benefits were limited and some participants didn't experience any perceived benefit from TENS. With further exploration during the discussions, common issues were uncovered including patient expectations and ease of use of the device. Future studies should aim to investigate TENS as a possible intervention for IC as it shows promise. However, the issues described should be addressed. Patient expectations need to be more closely managed along with improvements in the design of the device.

## 11.4: DISCUSSION

---

### 11.4.1: Background:

---

The literature surrounding the experience of living with PAD and IC will now be summarised in an effort to place the results from the current study in context.

Table 11.4 summarises the findings of previous studies next to those from the current study. The earliest reported qualitative analysis of PAD and IC was that by Gibson and Kenrick (1998). They interviewed 9 participants, 3-18 months post-surgery and used grounded theory to identify the themes related to the experience of living with PAD. 'Pain', 'powerlessness', 'someone else's problem' and 'shrinking horizons' were identified as themes in the context of the disease process (Table 11.4).

Treat-Jacobson et al (2002) investigated the patient perspective on health-related quality of life. Thirty-eight patients with PAD were interviewed regarding their experience of living with the disease and the nature of the effect on their quality of life. The transcripts were analysed using a grounded theory approach and seven themes emerged (Table 11.4).

Wann-Hansson et al (2005) continued the trend with a qualitative study where 24 patients at varying stages of the disease were interviewed about their experience of living with PAD. The interviews were conducted with specific reference to waiting for surgical intervention and three main themes were identified (Table 11.4). In a similar study, the same authors conducted a study where 14 patients were interviewed at 6 months, and 2 ½ years post-surgery (Wann-Hansson et al 2008). Both of these studies, in contrast to the previous, used manifest and latent content analysis to examine the data collected. Again, three main themes were identified and these related to the aims of the study i.e. the experience of PAD post-surgery (Table 11.4).

Galea et al (2008) used focus groups to identify barriers and facilitators to walking in patients with IC. They identified a number of personal and environmental factors that contributed to walking activity in this population (Galea et al 2008). The evidence and

rationale for walking was well summarised indicating that walking helps to prevent disease progression, increase walking distance (pain-free and maximal) and contributes to an overall increase in physical activity (Galea et al 2008).

Egberg et al (2012) conducted the only qualitative study to focus on the experience of solely patients with IC. Interviews were employed with 15 patients that aimed to garner their experiences of pain, mobility, daily life and social life (Egberg et al 2012). Thematic analysis was conducted on the transcribed data and 6 themes were identified (Table 11.4).

The current study is the only one that employs focus group discussion to gather the original data. Similar to Egberg et al (2012), only patients with IC were included but the text was analysed using content analysis in the same manner as Wann-Hansson et al (2005; 2008). The themes emerging from the current study are now discussed and compared in turn to the findings of these and other studies of the experience of living with PAD.

Table 11.4: Summary of main themes identified in studies on the experience of living with PAD and IC

Study	Gibson and Kenrick (1998)	Treat-Jacobson et al (2002)	Wann-Hansson et al (2005)	Wann-Hansson et al (2008)	Egberg et al (2012)	Current Study
<b>Participants</b>	9 patients with PAD who had bypass surgery in the past 18 months	38 patients with PAD- varying severity (IC, rest pain and ulcers)	24 patients with PAD- varying severity (IC, rest pain and ulcers) 75% ischaemic ulcers	14 patients with PAD at 6 months and 2.5 years post-surgery	15 patients with IC	6 patients with IC
<b>Data collection and Analysis</b>	Interviews Grounded Theory	Interviews Grounded Theory	Interviews Manifest and latent content analysis	Interviews Manifest and latent content analysis	Interviews Thematic analysis	Focus Group Manifest and latent content analysis
<b>Themes Identified</b>	Pain Powerlessness Someone else's problem Shrinking horizons	Delay in diagnosis and frustration with management Pain Limitation in physical functioning Limitation in social and role functioning Compromise of self Uncertainty and fear Adaptation to the effects of the disease and demonstration of resiliency	Being limited by the burden Striving to relieve the burden Accepting and adapting to the feeling of the burden	Becoming better but not cured Recapturing control over life Reappraising meaning in life (post-revascularisation)	Experiencing leg discomfort Moving around in a new way Feeling inconvenient when forced to stop Missing previous life Incorporating IC in daily life To lead a strenuous life	Frustration Pain Limited physical and social functioning Acceptance, adaptation and control of the pain and disease Knowledge and understanding

---

#### 11.4.2: Themes:

---

##### 11.4.2.1: Frustration

---

The feelings of frustration expressed by the current study participants seem to be common across previous studies. Frustration was identified related to a number of aspects of the disease. Treat-Jacobson et al (2002) found that physical, psychosocial and emotional disability and a lack of control over the disease lead to frustration, helplessness and despair. Galea et al (2008) in a study of barriers and facilitators to walking with PAD found that participants describe feelings of frustration and unease relating to 'being noticed' by others when stopping for a rest. This finding, related to others' understanding of the disease and their associated embarrassment was also highlighted by Wann-Hansson et al (2005). They found that irritation and frustration were expressed related to the fact that other people were unaware of the pain and suffering and this has an impact on relationships.

Gibson and Kenrick (1998) proposed a link between coping strategies employed and frustration. They suggested that people undergoing surgery may use passivity, dependency and lack of knowledge as coping strategies since trying to be in charge of a situation that they cannot control may lead to frustration (Gibson and Kenrick 1998).

These sources of frustration could be minimised through educational strategies. With more knowledge and thus understanding by patients and their significant others, feelings of frustration may be reduced (Williams et al 1998; Schillinger et al 2002; Gazmararian et al 2003).

##### 11.4.2.2: Pain

---

Pain was found to be the most influential factor in patients' everyday life (Wann-Hansson et al 2005). Everything revolved around strategies to relieve pain and reduce the impact on daily life.

'Pain', 'a burden' or 'leg discomfort', were identified as major themes in a majority of the studies (Table 11.4). Pain was the most common symptom reported by participants, it was found to be unpredictable and had a great impact on daily life (Wann-Hansson et al 2005). The pain was described as a cramp and could be visualized as "a rope being pulled tighter



and tighter, as if the leg were being twisted, or being blown to pieces, or that it hurt so much that they felt nauseous” (Egberg et al 2012 p6) and burning, throbbing, pressure, bursting, stabbing and a terrible cramp (Wann-Hansson et al 2005).

Strategies to relieve or cope with pain were also a major component of the discussions. Behavioural coping strategies have been identified as stopping for a rest, massaging their leg, limping, massage; rubbing, smearing the foot and touching (Wann- Hansson et al 2005; Galea et al 2008). Cognitive strategies for coping with pain included ignoring it, distracting or diverting attention and positive self-statements (Galea et al 2008). These are similar to those implemented by individuals with other pain syndromes (Boothby et al 1999). These strategies to relieve pain and promote circulation were interpreted as fostering a sense of control (Wann-Hansson et al 2005).

Similar to the current study, patients did not like taking analgesics for pain either due to side effects or because they were ineffective and they preferred to find alternative strategies (Wann-Hansson et al 2005).

Patients with PAD generally believe that walking is good for PAD/IC but confusion regarding the benefits or harm caused by pain during walking is a commonly reported issue (Galea et al 2008). They are unsure of the extent to which pain should be tolerated and what effect it is having (Galea et al 2008). This was also demonstrated in the current study. For patients with IC, walking acts as both a stimulus and a therapy for pain. This results in exceptional circumstances for engaging in walking (Galea et al 2008). If the pain can be reduced, even just a little bit, it might help them engage with the essential therapy that is walking.

Further information regarding the nature of the pain and how these patients cope with it is required (Wann-Hansson et al 2005). Nevertheless, it seems that education regarding the mechanisms of pain and simple, pain-relieving interventions might help to reduce the pain-related fear they experience (Asmundson et al 2004).

#### 11.4.2.3: Limited physical and social functioning

---

PAD is a chronic experience with lifestyle changes and associated with a physical, social and emotional burden (Wann-Hansson et al 2005; Egberg et al 2012). Limitations in social activities resulted in a loss of interest and inspiration and contributed to involuntary isolation and huge emotional strain (Wann-Hansson et al 2005; Egberg 2012). This did not seem to be the case in the current study. Participants described a great interest in social activities, they just felt they could not do them or when they did, their performance was unsatisfactory.

Scheduled walking sessions and supervised exercise programmes offer structure and consistency, motivation and companionship of like individuals (Galea et al 2008). Having a walking partner who understands the need for taking rest breaks and what is happening with the disease helped patients overcome the pain (Galea et al 2008). This relates to the need for information and education for families and significant others along with organised and structured walking groups or exercise classes.

Wann-Hansson et al (2008) suggested that age could be a contributing factor to the decrease in physical and social function.

#### 11.4.2.4: Acceptance, adaptation and control of the pain and disease

---

The experience of living with PAD can be seen within the concept of transition (Wann-Hansson et al 2008). Essential properties of the transition process for chronic conditions are: awareness, engagement, change and difference, time span, critical point and events (Meleis et al 2000). Awareness relates to education and understanding of the condition and the realistic expectations of recovery. Engagement and change require appropriate coping strategies and acceptance of adaptation e.g. change in hobbies or method of completing ADLs. This has to occur over time and there will be crucial points where patients' continuation will be challenged. Egberg et al (2012) found that the disease and disability is hard to accept for patients with PAD and IC due to the nature of the symptoms: they feel, and appear to others, healthier than they actually are. This is an important aspect to

address with tailored education strategies that stress the severity of the disease and with a focus on the presence of systemic, progressive atherosclerosis. Wann- Hansson et al (2008) found that post-surgery, patients did realise over time that the condition was probably not going to get better and this made them focus on at least not getting worse. This supports the proposition that challenging patient expectations and helping them engage with the chronicity of their disease could have positive effects on their engagement with self-management strategies (Lawn et al 2011).

A focus on curative measures (surgery) may affect patients' perceptions of their disease leading them to expect a cure and limit 'acceptance' (Gibson and Kenrick 1998). Currently, the medical system manages PAD as an acute illness as evidenced by the modes of treatment and the lack of structured rehabilitation, education and support to facilitate patients' adjustment to their illness (Gibson and Kenrick 1998; Wann-Hansson et al 2008). Beliefs that focus on a passive 'cure' or some type of 'fix' have been found to independently predict poorer functioning in patients with chronic pain (Turner et al 2000). These beliefs may have been reinforced by the current study. This study was focussed on a device that passively intervenes to reduce their pain; TENS therefore may reinforce these types of beliefs. Further study of interventions for IC should include an educational component where participants' beliefs about their disease and the pain are explored and unhelpful beliefs challenged.

Management of coronary artery disease includes well-established physical and psychological rehabilitation interventions and thorough education and understanding of patients and the general population. This method of management has been shown to encourage acceptance and empowerment leading to successful self-management (Dusseldorp et al 1999). Further focus on these principles of management in the PAD population is required as the current medical care and reliance on medications/surgery may evoke a feeling of helplessness and lack of control (Miller 2000).

Effective coping strategies result in containment of uncomfortable feelings, generation of hope, enhancing of self-esteem, maintenance of relationships and maintenance of health status (Miller 2000). Trying to do the best to prevent further deterioration has been found to be a strategy that patients use to gain a sense of control of their disease (Wann-Hansson et al 2008). The most important 'rule' for patients' with PAD and IC is to stop smoking and this could be seen as a coping strategy as it is one thing which the patient alone can control (Gibson and Kenrick 1998).

In terms of walking, cognitive and behavioural pain-coping strategies were the most frequently mentioned facilitators for walking (Galea et al 2008). Companion and walking partners have been shown to provide a source of emotional support, primarily through verbal persuasion (Galea et al 2008). Support for patients with PAD should therefore include strategies to maintain a sense of normality, along with a focus on keeping symptoms under control with information about behavioural changes such as risk factor modification, exercise therapy and structured education programmes (Wann-Hansson et al 2005).

#### 11.4.2.5: Knowledge and understanding

---

Patients with PAD waiting for intervention have difficulties with coping with self-image and functioning, feelings of depression, frustration and uselessness and need to have a sense of control over the future (Leech 1982 as cited by Wann-Hansson et al 2005). It is therefore important to manage patients' expectations prior to treatment with information and education regarding the course and progression of the disease thus reducing stress and anxiety (Wann-Hansson et al 2005). Galea et al (2008) found that correct information from medical practitioners resulted in social coping strategies and increased the motivation to walk. Instructions to walk were heeded when the benefits were explained clearly i.e. walking will help to prevent further progression, not cure your disease (Galea et al 2008).

The experience of living with PAD has been shown to result in a need to 1) understand, 2) adapt and 3) accept the physical limitations of the disease (Wann-Hansson et al 2005). However, questioning advice provided might entail acknowledging doubts in the efficacy of

the treatment (Gibson and Kenrick 1998). This obstacle was combated by use of social support and reasoning or accepting that the powerlessness and decrease in quality of life were a result of 'old age' (Wann-Hansson et al 2005).

Participants' uncertainty about the condition and lack of knowledge pertaining to the benefits of walking for intermittent claudication are cognitive barriers for engaging in regular activity (Galea et al 2008). Collins et al (2011) investigated the effects of a video-based educational experience on knowledge of PAD and adverse events, dietary habits, and exercise behaviours. They found that a series of 4 videos increased self-report knowledge of 1) the disease and possible cardiovascular events, 2) risk factors, 3) the fact that walking is beneficial and 4) that poor circulation is a disease (Collins et al 2011).

Uncertainty and fear of doing something wrong when walking in pain affected patient adherence to exercise at the initial stages post diagnosis but over time it became more of a routine (Wann-Hansson et al 2008). One way to gain control was to assume the expert role regarding taking medicines, exercising, bandaging wounds and seeking information about PAD (Wann-Hansson et al 2008).

An increase in knowledge and understanding can help patients with PAD accept the chronicity of the disease. Wann-Hansson et al (2008) identified a change of roles when chronicity was accepted where spouses took control over chores and getting a cleaner/gardener helped to make life more manageable. This was hard at first but works well when transition process is completed and is less likely to encourage feelings of frustration (Wann-Hansson et al 2008).

Information and education must include 'downwards comparisons' (the ability to compare oneself favourably to another in a similar situation) and family or significant others to help minimise the impact of PAD on their lives and increase the efficacy of intervention (Wann-Hansson et al 2008). Downwards social comparison is the theory that someone who is "experiencing negative affect can enhance their subjective through comparison with a less

fortunate other” (Wills 1981, p 245). In the case of patients with PAD and IC, this might be through comparison with another person with PAD and IC whose disease is more progressed. Also, increased knowledge and understanding about the prognosis of their disease by the patient and their significant others may help to foster a sense of control over their condition, if not their prognosis.

---

#### 11.4.3: Strengths and Limitations of the Study:

---

The purpose of this study was to explore the experience of patients with PAD and IC using TENS at home. It was hoped that the findings could inform further investigation of TENS for PAD and IC and provide an insight into the possible clinical use of TENS for IC pain.

As the use of TENS in patients with PAD and IC had not previously been investigated, there was no established method for investigation or comparison. This study was designed as a pragmatic, follow-up investigation with the aim of generating descriptive and clinically informative data.

The outcomes of the study support previous investigations of the experience of living with PAD and IC, highlighting a condition characterised by feelings of frustration. These negative feelings were commonly associated with pain but also with accepting and adapting to a chronic illness and adjusting to limited physical and social functioning. The experience of using TENS was characterised by feelings of benefit and usefulness but also disappointment at the lack of comprehensive analgesic effect. These are novel and informative findings. However, there are a number of methodological choices that have impacted on their credibility, transferability and dependability.

The sample recruited to this study was selected to reflect patients with PAD and IC that would likely be provided with a TENS machine in a clinical situation. TENS is commonly provided to those who express an interest and who are suitable for the intervention. It is also provided only after a trial period that tests for efficacy. Purposive, pragmatic sampling included participants who participated in a treadmill study of TENS for IC (Chapter 9). All

participants were invited to participate in a 'follow-up' phase of the study and the first six to reply were included. This method of sampling was chosen as the participants included in the clinical study met the inclusion criteria of patients with stable Fontaine stage II claudication, limited comorbidities and no contraindications to TENS stimulation. Recruiting in this manner also imitated the clinical setting. The treadmill study could be considered as the trial period and the method of including those first to respond imitated patients indicating interest in trying TENS. These sampling choices allowed the study to reflect the clinical situation and thus increase the credibility or ecological validity of the study however they may have had a negative effect on transferability.

This manner of recruitment that purposively included those who had already experienced TENS and who were most interested in trying TENS at home could have resulted in the collection of disproportionately positive experiences of using TENS at home. Their inclination towards trying TENS may have predisposed them to report positive experiences. The study findings may therefore not be typical and representative of all patients with PAD and IC.

Conversely, these recruitment strategies may have targeted those who were most desperate to find a solution for their pain and thus were most interested to try TENS. These participants may therefore be characterised by more severe experiences of pain and/or a poor state of coping with their condition. These factors may have led to more negative experiences reported if TENS did not represent the relief for which they were searching. To address these potential challenges to the credibility, transferability and objectivity, future studies should attempt to recruit a more diverse sample and elicit the experiences of a wider range of patients with PAD and IC.

Another factor that may have detrimentally affected the credibility of the findings of this study is the inclusion of the primary researcher as the focus group moderator. As the researcher conducted all aspects of the studies, the participants may not have discussed their use of TENS with the same, unbiased honesty if an independent researcher had

moderated the focus group. The participants may have felt that they did not want to cause 'disappointment' by discussing and recording negative experiences.

Nevertheless, by acting as the focus group moderator the primary researcher was in the ideal position to help direct the discussion and probe what they felt were particularly pertinent points. An independent researcher with less knowledge and understanding of the clinical condition and the research field may have failed to take the same opportunities. Therefore, using the primary researcher acting as the focus group moderator could also be considered a strength of this study as it may have allowed further exploration and elucidation of important aspects of the experience of using TENS for PAD and IC.

On reflection, this connection with the study and understanding of the clinical area by the focus group moderator could have had additional negative effects on the generation of data and credibility of the study. As the moderator of the focus group was invested in the study, they may have inadvertently affected the discussion by directing it towards positive aspects of the experience of using TENS. This may have biased the findings of the study towards positive effects of TENS. Conversely the researcher, being cognisant of their positionality, may have directed the discussion towards the negative aspects by overcompensating. For future studies, it is important that the moderator of the focus group is an independent researcher so that there is less chance that their positionality may affect the data collection. Nevertheless, this independent researcher should possess a depth of understanding surrounding the clinical condition (PAD and IC) and also experience of using TENS.



### 11.5: CHAPTER 11 SUMMARY:

---

This study sought to investigate the experience of using TENS at home for daily life with PAD and IC. The findings support the previous work describing the experience of living with PAD and IC: a life characterised by feelings of frustration associated with pain, accepting and adapting to a chronic illness and adjusting to limited physical and social functioning. The experience of using TENS for IC was characterised by benefit but also disappointment. Different patients had different experiences that seem to be determined primarily by expectations and underlying walking ability or physical functioning. This is the only study to date that explores the experience of using TENS for IC and also the only known qualitative study on PAD and IC that utilises a focus group methodology.

Overall this study adds a unique perspective to the literature in this area and highlights possible areas for future research including the potential therapeutic potential of TENS as an adjunctive, self-management intervention for PAD and IC.

## CHAPTER 12: GENERAL DISCUSSIONS AND CONCLUSIONS:

---

### 12.1: AIM OF CHAPTER 12:

---

Research has shown that IC is a complex, chronic pain problem that is associated with decreased physical and psychological function and decreased quality of life in patients with PAD. Despite good medical management of IC (risk factor reduction, exercise and pharmacological therapy), the problems of reduced adherence to exercise therapy and inadequate relief of pain remain, and continue to limit optimal outcome from current management. Poor adherence to exercise therapy, for example, leads to an increase in the risk of morbidity and mortality, especially from associated cardiovascular complications.

This programme of research examined the efficacy of TENS as a safe, adjunctive therapy for IC. TENS is a possible adjunctive intervention for IC pain and if successful could prove to be a useful, inexpensive, non-pharmacological intervention that reduces the experience of IC pain and/or improves walking performance. TENS may therefore help to increase adherence to exercise therapy, and by so doing, reduce the chance of patients progressing to develop more serious cardiovascular disease.

The research programme also examined the subjective descriptions of IC pain, which currently is an unknown factor, because these may be of assistance in designing and determining the efficacy of therapies for IC.

A literature review was therefore conducted to establish the current state of the relevant evidence base. Figure 12.1 reminds the reader of the rationale for the directions taken during this programme of research. A chapter-by-chapter summary of key points emerging from the literature review is given, along with the subsequent research questions.

**Chapter 2: Peripheral Arterial Disease and Intermittent Claudication**

- PAD and IC are common and associated with negative psychosocial health and a decrease in quality of life
- The pain associated with IC is poorly understood and current management appears lacking

**Research Questions Identified:**

- What qualities characterise the subjective description of IC pain?
- How does pain affect walking performance in patients with PAD and IC?
- How do the psychosocial aspects of IC pain affect walking performance?

**Chapter 3: Pain**

- Pain is a complex, multidimensional experience, unique to the individual and influenced by numerous physiological, psychological, cultural and environmental factors
- Pain syndromes are characterised by certain clusters of subjective descriptors that can be recorded using the vocabulary of the MPQ
- The subjective descriptors that classify IC pain, or ischaemic pain, have not been comprehensively reported in the published literature

**Research Questions Identified:**

- What qualities characterise the subjective description of IC pain?

**Chapter 4: Transcutaneous Electrical Nerve Stimulation**

- TENS is a cheap, non-pharmacological intervention that has been shown to reduce pain and increase function in patients with chronic pain
- TENS has not been tested for IC pain

**Research Questions Identified:**

- What are the effects of TENS on measures of pain and walking performance in patients with IC?
- How do the different types of TENS affect walking performance in patients with IC?

**Chapter 5: Laboratory Induced Pain**

- Laboratory induced pain has many functions including: assessment of analgesic efficacy; studies of psychological variables and constructs and evaluation of the underlying mechanisms of pain and hypoalgesic interventions
- One common method of inducing pain is the SETT, which induces ischaemic pain in the upper limb of healthy volunteers
- TENS has been shown to reduce pain intensity during the upper limb SETT. However, due to the physiological and functional differences between the upper and lower limbs, the effects of TENS on lower limb induced ischaemic pain need to be investigated before extrapolation of these results to a clinical IC population
- Initial work has been completed on a lower limb method of induced ischaemic pain

**Research Questions Identified:**

- Does the modified lower limb SETT induce reliable experiences of pain in healthy volunteers?
- What subjective qualities are associated with lower limb, laboratory induced ischaemic pain in healthy volunteers?
- Is laboratory induced, ischaemic pain in the lower limb comparable in quality and intensity to clinical IC pain?
- What are the effects of TENS on induced ischaemic pain in the lower limb of healthy volunteers?

Figure 12.1: Flow diagram summary of the literature review and the research questions developed from this review

Two broad research questions were identified as encapsulating all of the above and thus were addressed within this thesis:

1. What qualities characterise the subjective description of IC pain?
2. What are the effects of TENS on measures of pain and walking performance in patients with IC?

These two questions led directly to the two aims of the project: 1) to investigate the subjective description of IC pain and 2) to investigate the effects of TENS on measures of pain and walking performance in patients with IC. These aims were addressed through a series of studies previously described and discussed within this thesis, which included clinical and laboratory investigations in healthy volunteers.

This chapter will present the central discussions and conclusions of this thesis. The main findings of the research programme will be discussed in relation to the research aims. Conclusions regarding these findings will be offered and implications and recommendations discussed. The limitations of this programme of work and how these limitations have affected the conclusions drawn will also be discussed.

## **12.2: SUMMARY OF KEY FINDINGS FROM THE CURRENT PROJECT:**

---

The findings of this project will be summarised in relation to the separate studies and with reference to the research aim to which they contribute.

The first study was the validation study of the mSETT, developed to induce ischaemic pain in the lower limb of healthy volunteers. The purpose of the study of mSETT-induced pain was to contribute towards the first research aim: to investigate the subjective description of IC pain. The mSETT procedure was developed with the purpose of creating a pre-clinical model of IC pain and was found to reliably induce pain in the lower limb of healthy volunteers. Test-retest reliability was established over two occasions in terms of time taken to report pain threshold, tolerance, and for pain endurance.

By completing a post-hoc analysis on MPQ data collected in the laboratory and clinical studies, the first research aim was addressed. The reports of ischaemic pain recorded using the MPQ in participants with PAD and IC and from healthy volunteers experiencing the mSETT, compared the subjective qualities of the two pain experiences. A cluster of adjectives (3 sensory-discriminative, 1 affective-motivational, and 2 cognitive-evaluative) characterised the IC pain experience. These adjectives are similar to those used to describe nociceptive pain related to an ischaemic environment and correlate with words used anecdotally to describe IC in the clinical literature. The pain experience associated with the mSETT was similar in quality to that reported by patients with PAD and IC. Laboratory pain was however rated as being more severe and intense than clinical IC pain as measured by the MPQ. This suggests that although inducing pain that is similar in quality i.e. through the same neurophysiological mechanisms, the parameters of the method require modification prior to being accepted as a model of IC pain.

The second laboratory study addressed the second research aim. The mSETT procedure as developed in the first study was employed to test the effects of HF-TENS on lower limb laboratory ischaemic pain. These effects were compared with P-TENS in a repeated measures design. HF-TENS was found to increase time to report pain threshold, tolerance and pain endurance compared to No-TENS control and P-TENS. Pain intensity was reduced with HF-TENS from the 3<sup>rd</sup> to the 8<sup>th</sup> minute during testing compared to baseline and this effect was found to be greater than P-TENS in the 3<sup>rd</sup> minute and then from the 5<sup>th</sup> to the 8<sup>th</sup> minute. For pain quality, mean sensory, reactive and total PRI scores of the MPQ were reduced with both TENS interventions (P-TENS and HF-TENS). No difference was found between the groups. It was concluded therefore that HF-TENS has hypoalgesic effects on induced ischaemic pain in the lower limb of healthy volunteers.

A clinical study of TENS for pain and walking performance in a sample of participants with PAD and IC was conducted to address the second research aim. Forty participants with PAD and IC were recruited from a claudication outpatient clinic to participate in a phase IIa, 'proof of concept' study. The effects of HF and LF-TENS compared to P-TENS were

investigated in a repeated measures design. In relation to walking distance, HF-TENS was found to increase time to ICD, FCD and ACD compared to P-TENS. Only ACD increased with LF-TENS compared to P-TENS. In a between-group comparison, HF-TENS was found to increase ICD more than LF-TENS. However, no difference between the groups was found for FCD or ACD. When the data were pooled and the effects of 'TENS intervention' analysed, significant changes in ICD, CD and ACD were found with a median change in ACD of 35.5m compared to P-TENS. Positive relationships were observed between all measures of walking performance (ICD, FCD and ACD) indicating a common, consistent development of pain over time. Positive relationships were also found between baseline measures of FCD, ACD, WIQ and PSEQ. Negative relationships were observed between PCS and PSEQ, PRI and PSEQ, BMI and PSEQ and PCS and WIQ. For the experimental measures, the only positive relationships were observed between  $\Delta$ ICD and BMI and between  $\Delta$ ACD and change in TENS intensity. No relationships were found however, between either the most common physiological measure of PAD and IC severity (ABPI), or measures of pain intensity (PRI) and measures of walking performance. This suggests that walking distance in patients with IC is not related to disease severity and pain intensity. Multiple regression analysis was performed on ACD and  $\Delta$ ACD. Significant models were produced that explained variance in both variables. No variable was found to independently predict ACD. However, change in TENS intensity was found to predict  $\Delta$ ACD.

The following overall conclusions can be drawn from the results of this 'proof of concept' study: TENS is associated with an increase in walking performance in patients with PAD and IC, with HF-TENS being more effective than LF-TENS. The effect of TENS therefore merits further investigation in this population. The results of the correlations and regression analysis also warrant further investigation. These data suggest a central role of pain and its associated psychosocial factors in walking performance for patients with PAD and IC.

In addition to the original aims of the programme of research, a study was conducted with a small sample of participants from the original clinical study. TENS had been shown to improve treadmill walking performance for patients with PAD and IC. However, an

important question arising from the research was: if provided with a TENS machine and training for use at home, do patients with IC use the device and do they feel it is a useful adjunctive intervention for their pain? A pragmatic, qualitative follow-up study was designed and six participants were recruited from the original clinical cohort. The experience of living with PAD and IC was found to be characterised by feelings of frustration related to pain, decreased walking ability, decreased quality of life and poor knowledge and understanding of the disease. The experience of using TENS at home for PAD and IC was characterised by general feelings of benefit but also disappointment. Unrealistic expectation of effect was a common theme along with ease of use. Overall, TENS was judged to be of benefit for daily life with PAD and IC although further study is required to explore the issues identified and to investigate any benefits in terms of health and quality of life.

### 12.3: GENERAL DISCUSSIONS:

---

The following section aims to discuss the general findings of the studies included in this programme of research. The implications of these findings for clinical practice and further research will be explored with special reference to how they relate to other research conducted in the area. The limitations of this programme of research will also be addressed. Finally, overall conclusions will be presented to complete the thesis.

---

#### 12.3.1: General Findings Related to Research Aim 1:

---

##### 12.3.1.1: The pain experience of IC is characterised by specific descriptive adjectives and the mSETT could provide an adequate laboratory representation

---

When investigating the effect of a painful condition on patient quality of life, or when designing interventions for painful conditions, an understanding of the sensations that are to be reduced is helpful (Dubuisson and Melzack 1976; Galer et al 2000; Holtan and Kongsgaard 2009). Similarly, to interpret the effect of an intervention requires investigators to have an appreciation of the different components of the pain experience. This understanding commonly stems from an appreciation of the subjective description of the pain experience. Prior to the commencement of this research programme, the subjective description of the pain experience of IC had not been investigated. Thus, the results of these

investigations of the IC pain experience could help improve the understanding of the multidimensional nature of IC pain and inform the investigation of novel therapies that target IC pain.

The examination of IC pain in this thesis involved recording patients' reports of pain immediately after completing a maximal treadmill test (Chapter 10). Analysis of these reports identified a group of adjectives that seem to characterise the experience of IC pain. This exploration of IC pain represents an important step towards a greater understanding of the pain experience.

A similar investigation was also conducted in laboratory-induced lower limb ischaemic pain with the aim of developing a pre-clinical model of IC pain (Chapter 10). MPQ descriptions of pain were recorded from healthy volunteers immediately after completing the mSETT procedure. The adjectives selected were compared to those selected by patients with IC and analysed for similarities and differences. The results showed that when describing mSETT-induced pain, healthy volunteers commonly chose adjectives that were similar to those selected by patients with IC pain. They did however tend to select adjectives that described a more intense pain, similar to that recorded in patients with more progressed lower limb atherosclerosis and profound ischaemia. These findings suggest that the mSETT procedure successfully induces ischaemic pain although it seems to be more severe than that experienced by patients with IC.

As discussed in Chapter 10, the differences between the two pain experiences are most likely due to the mechanisms and situational aspects of induction. The degree of ischaemic environment created using the mSETT method is readily manipulated (Pertovaara et al 1984). Thus slight changes in the parameters employed in the mSETT may result in an experience that is more similar to IC pain. These changes could address the differences in the sensory-discriminative aspects of the pain experience. The affective and evaluative aspects of the clinical pain experience will be harder to match in the laboratory situation. However, this inability to match the affective and evaluative components of the pain



experience is one of the cornerstones of experimental models of pain. The advantage of experimental pain is the ability to induce pain that is unaffected by the confounding comorbidities and psychological aspects of disease present in clinical pain. Therefore it is unrealistic and somewhat counterproductive to strive for a model of induced lower limb ischaemic pain that mirrors the affective and evaluative components of IC pain.

#### 12.3.1.2: The mSETT is a reliable method of inducing lower limb ischaemic pain in a small sample of volunteers

---

One of the aims of this research programme was to develop and evaluate a method of inducing ischaemic pain in the lower limb of healthy volunteers. The mSETT method described in Chapter 7 achieves this aim by inducing consistent and safe levels of pain, albeit in a small sample. Test-retest reliability was established over two occasions and the quality of pain induced was also explored and compared to clinical ischaemic pain.

No published study has attempted to develop such a method. There are no previous reports of the test-retest reliability of any experimental ischaemic pain method. Therefore the findings of this study have value as a new laboratory method of inducing lower limb ischaemic pain.

The current examination of this method is within a small sample ( $n = 11$ ). Pain measurements were only examined over two occasions and no inter-rater reliability was assessed. A reliable method could provide a laboratory model of IC pain and be used to examine the interaction of the pain experience with daily tasks and interventions. Also, as a laboratory model of ischaemic pain, this can be used in the same way as the upper limb SETT has been employed. For example, it can be used for the testing of analgesic interventions (Smith et al 1966; Posner 1984; Benedetti 1996; Amanzio and Benedetti 1999). It can also be employed for laboratory testing of the relationships between psychosocial variables and the experience of pain e.g. attention and fear of pain (Moore et al 2013). Moreover, the method can be used for examining the effects of TENS parameters (Claydon et al 2011; Chen and Johnson 2011); similar to the study described in Chapter 8 of

this thesis. This first development of the mSETT is a unique contribution to laboratory of pain and for ischaemic disease.

#### 12.3.1.3: Psychosocial variables correlate with walking performance in patients with IC

---

The pain experience of IC is thought to be a central determinant of walking performance in patients with PAD (Hiatt 2001; Egberg et al 2012). In the current study however, the central role of pain intensity in determining walking distance in patients with PAD and IC was not comprehensively supported. The analysis of relationships between variables in the clinical study found no direct relationships between pain intensity (PRI score) and ACD. Clinical thinking based on a biomedical model of health (related to the relationship between pain intensity and function) would predict a strong relationship between the two as ACD is conceptualised as a measure of pain tolerance (Oka et al 2006). However, the biopsychosocial literature on chronic pain has shown a central role for psychosocial variables in the pain experience of chronic disease. These results therefore point to the need to examine psychosocial measures related to disease, pain and function in IC.

The measures found to be related to ACD were WIQ score ( $r_s = -.46$ ,  $p = 0.005$ ) and PSEQ score ( $r_s = 0.37$ ,  $p = 0.026$ ). The WIQ is a self-report assessment of walking ability that is closely correlated with treadmill walking measures (Regensteiner et al 1990; McDermott et al 1998). Therefore these results were expected. The conclusion regarding this observed relationship is that the participants in the study are accurate in estimating their walking ability and the questionnaire records this sensitively.

Despite the lack of relationship between pain intensity and the clinical variable ACD, the positive relationship between PSEQ and ACD indicates that pain beliefs related to self-efficacy (a motivating aspect of the pain experience) play a central role in walking performance in patients with PAD and IC. PSEQ score is a measure of the responder's confidence, or self-efficacy, in their ability to perform tasks despite their pain (Nicholas 2007). The positive relationship between this and ACD suggests that a patient with PAD and

IC who has increased self-efficacy beliefs related to their pain, walks a greater distance on the treadmill.

In general, these results confirm the lack of strong associations between biomedical variables and pain intensity in chronic disease. They do however indicate a central role for psychosocial variables in mediating between pain and functional performance.

As discussed previously, pain is a complex experience, not just defined by the intensity of the experience. Associated psychosocial factors, and particularly self-efficacy, have been shown to have significant effects on many aspects of health and function across a variety of pain conditions (Keefe et al 2004; Turner et al 2005; Woby et al 2007; Nicholas 2007). The unique results of this programme of research indicate that psychosocial factors and predominantly pain self-efficacy are also influencing factors on walking performance in patients with PAD and IC.

These results can now add to the growing evidence that psychosocial factors play a major role in the experience of PAD and IC, and in influencing the outcomes from exercise therapy. Depression has been identified as a common negative psychological feature of PAD and IC (Smolderen et al 2008; Garnefski et al 2009). Pain self-efficacy can now be identified as a positive variable in PAD, which may help to counteract depression in coping with PAD and IC. Collins et al (2010) and Sol et al (2011) have shown the important role of general self-efficacy beliefs in patients with PAD. Neither of these studies however, reported on pain-related self-efficacy as identified in the current programme of research. The self-efficacy measure chosen for this study is a psychometrically designed measure for illuminating self-efficacy specifically for completing activities despite pain (Nicholas 2007). The use of this measure in this research programme has allowed identification of the role of pain-specific self-efficacy in patients with PAD and IC.

Finally, although pain catastrophising has been found to be important in certain musculoskeletal pain conditions (Quartana et al 2009), this was not found to be the case for

the patients in the present study. One explanation may be that catastrophising has less influence for patients with PAD as they have grown very used to their daily pain problem and thus do not develop catastrophising thoughts to the same degree as those with other chronic pain syndromes. For example, patients with back pain have often had their lives suddenly interrupted by pain and a sudden decrease in function. These patients have been shown to exhibit high levels of pain catastrophising (Buer and Linton 2002). Patients with PAD, on the other hand, experience a more gradual development of pain and loss of function. They also experience IC pain daily, perhaps hourly, on movement. Patients with PAD may have adapted more to the condition and thus avoid the extremes of pain catastrophising.

As said before, these findings are from a small sample, are recorded with self-report measures that are not designed for use in IC pain and employed in a cross-sectional design. A future study could investigate the influence and relationships between these psychosocial factors in a larger, longitudinal study of patients with PAD and IC. This type of investigation could further elucidate the specific relationships between these psychosocial variables and pain and function whilst also possibly providing indications of causality. Such a study could also be combined with the adaptation of questionnaires to test these constructs specifically in an IC population.

#### 12.3.1.4: Living with PAD and IC is characterised by feelings of frustration

The findings of the follow-up focus group study replicate those of previous reports on the experience of living with PAD and IC (Wann-Hansson et al 2005, 2008; Galea et al 2008; Egberg 2012). However, this study identified patients' specific attention to pain, the consequences of this pain and their constant search for relief. In addition, the current study identified a lack of knowledge and understanding related to their disease and their pain. These features indicate a stronger focus on the impact of pain on the individual with PAD than has previously been the case. As such, they represent unique additions to our knowledge of living with PAD and IC pain.

An overriding feeling of frustration was a common characteristic of these experiences and may influence patients' ability to cope with their disease. The biopsychosocial approach to chronic pain has highlighted that negative emotions such as frustration (or negative mood such as depression) heightens the intensity of pain (Gatchel et al 2007). That individual patients seemed to be negatively impacted by their frustration suggested that their frustration was related to a decrease in motivation, which was in turn linked to a perceived lack of control over their pain and their disease. These findings are common amongst those with long-term conditions (Kennedy et al 2007) but have not been fully explored in PAD and IC. Addressing these complex emotions is not a simple task however; one common strategy employed with success is patient education and self-management (Lorig et al 2001, 2008; Macdonald et al 2008). Therefore, interventions that focus on empowering patients with PAD and IC through education and self-management may help them to gain some feelings of control over their pain and disease and reduce the negative feelings of frustration.

The results of this thesis therefore support the recommendation for structured self-management and patient education. However, this researcher, having worked with the patient sample, noted that this recommendation is currently not implemented effectively. Therefore patient education and self-management for patients with PAD and IC, with an emphasis on an understanding of the disease and coping techniques is required (Criqui 2001; Olin et al 2010). In addition to self-management and educational interventions that focus on their disease, education regarding pain is a crucial novel element that should be included. Development and evaluation of robust evidence-based strategies for improving patient empowerment through knowledge and understanding should be a priority for future research in PAD and IC (McDermott et al 2011).

#### 12.3.1.5: Summary:

The first aim of this programme of research was to investigate the subjective description of IC pain. By addressing this aim, unique and novel contributions have been made to research and clinical practice. Clusters of adjectives included within the MPQ have been identified as characterising the subjective pain experience of IC and laboratory induced lower limb

ischaemic pain. The mSETT method has been shown to be a reliable means by which lower limb ischaemic pain can be induced in healthy volunteers. In patients with IC, psychosocial variables and specifically pain-related self-efficacy beliefs have been found to be associated with walking performance. Finally, the experience of living with PAD and IC has been shown to be associated with feelings of frustration that seem to stem from a lack of understanding about their disease, their pain and the possibility of gaining relief from pain.

---

### 12.3.2: General Findings Related to Research Aim 2:

---

#### 12.3.2.1: TENS decreases mSETT-induced pain and increases walking performance in PAD and IC

---

Chapter 5 included a systematic review of the effects of TENS on induced ischaemic pain. The review found that despite variation in study design and TENS settings employed, HF-TENS is associated with hypoalgesic effects on induced ischaemic pain. The studies included in this review examined the effects of TENS on ischaemic pain in the upper limb. As part of this programme of research, the effects of HF-TENS were investigated on induced ischaemic pain in the lower limb of healthy volunteers as a precursor for investigating the effects of TENS on IC pain (Chapter 8). Compared to placebo, time taken to report pain threshold, pain tolerance and pain endurance all increased with HF-TENS, with mean changes of 24%, 52% and 64% respectively. These changes in intensity are comparable to those found by Chen and Johnson (2011) with similar TENS settings. An approximate mean reduction in pain intensity of 50% was observed with HF-TENS during the first 2 minutes of the upper limb SETT (Chen and Johnson 2011).

HF-TENS also appeared to affect all aspects of the IC pain experience in the clinical study indicating similar effects to those observed in the laboratory. The effects of LF-TENS were also examined in this population. Only the high intensity (tolerance/ACD) part of the pain experience was affected with LF-TENS stimulation. This suggests that LF-TENS had no effect on the less intense (ICD), or even 'near tolerance' (FCD) parts of the pain experience. Earlier research has suggested that this is a function of its extrasegmental mechanisms of action (Sluka and Walsh 2003). The most recent research however, refutes these assumptions and

has shown that HF and LF-TENS work through the same neurophysiological mechanisms (Radhakrishnan and Sluka 2005). The latent hypoalgesic effects have been reported to be a result of the higher stimulation intensity, rather than the difference in stimulation frequency (Lee et al 1985; Ma and Sluka 2001). It has been proposed that LF-TENS stimulation is more severe in sensation and thus actually augments the pain experience until the delayed descending mechanisms become effective (Chen and Johnson 2011). These proposed mechanisms could explain the effects of LF-TENS on IC pain seen in this study.

Since no other published study has examined the effects of TENS for patients with IC there are no results for direct comparison of effects. Most interventions for walking performance in patients with PAD and IC involve pharmaceutical therapy (Momsen et al 2009; Squires et al 2011), surgery (Frans et al 2011), a training regime (Mazari et al 2011) or complex interventions (Cunningham et al 2011).

A clinically meaningful improvement in walking distance for patients with IC is suggested to be an improvement of approximately 37% in ACD compared to placebo (De Backer et al 2009). In the current study, ACD increased by a median distance of 30m with HF-TENS and 23m with LF-TENS (13% and 18% change respectively). This is a modest change in walking distance and does not reach the reported clinically meaningful improvement. It is important to note however, that this clinically meaningful change is calculated using studies of interventions delivered over a period of time (3 to 12 months) (De Backer et al 2009). It could be considered that if delivered over a longer period of time, the initial improvement observed with TENS may increase to become clinically meaningful as participants' exercise performance improves with training and adjustment of TENS to the individual's optimal settings (Johnson et al 1991).

The only published literature regarding a similarly immediate and brief intervention for walking performance in PAD and IC is by Oakley et al (2008). The authors investigated the use of Nordic poles for walking performance in patients with IC. Pain-free walking distance (ICD) was found to increase by 52m (69% increase from baseline), and maximum walking

distance by 79m (38% increase from baseline) (Oakley et al 2008). This increase is greater than that found in the current study. However, due to the lack of placebo intervention, it is impossible to compare directly with the current study results. Also, the intervention is somewhat different. Nordic pole usage causes changes in the biomechanics of walking and thus the muscle groups used whilst walking will be altered. This means that the patients may not experience the full benefits associated with training of normal gait and thus the muscles will not be working in an ischaemic environment (Hiatt et al 1996; Beckett et al 2012). Nevertheless, irrespective of the benefits of other interventions for IC, the aim of TENS is to reduce the experience of pain and as such its use may be more likely in tandem with interventions like Nordic poles, medication, self-management and patient education.

In patients with IC and compared to P-TENS, ICD, FCD and ACD increased with HF-TENS and ACD increased with LF-TENS. However, no change in pain intensity was observed in either group. This indicates that even though the participants walked further, they were walking until pain reached the same intensity level. The results from this study suggest that TENS improves walking performance and encourages patients to walk further into the ischaemic environment.

#### 12.3.2.2: TENS has no effect on pain intensity despite increasing walking distance

The reasons why patients with IC reach walking intolerance have not been conclusively examined (Parr et al 2008). Current opinion is that tolerance is a result of haemodynamic changes in the lower limb leading to fatigue and pain (Hamburg and Balady 2011). Increasingly, published literature has failed to establish relationships between measurable haemodynamic and physiological variables and walking performance (Szuba et al 2006; Parr et al 2008; Kruidenier et al 2009a).

One central question is: is it pain, fear, muscle fatigue or something else that stops patients with IC from walking further? As reported in Chapter 8, HF-TENS increases time to reach pain threshold, tolerance and prolongs pain endurance in experimental ischaemic pain. This finding was replicated in the clinical sample (Chapter 9) where ICD, FCD and ACD increased



with HF-TENS intervention. No effect on muscle function has been found with TENS (Sluka and Walsh 2003). TENS has however, been shown to be effective at reducing ischaemic pain (Chen and Johnson 2011; Seenan et al 2012). These findings suggest that the increase in walking performance observed in this study is a result of TENS prolonging the time to pain tolerance. Consequently, this indicates that some aspect(s) related to the pain experience has a central role in the termination of walking in patients with IC.

This finding is also supported by the fact that in the current study, no change in pain intensity was found with TENS. The lack of reduction in pain intensity suggests that the participants stopped walking when they reached the same levels of pain on both occasions. The difference therefore was that with TENS, this level of pain occurred after a greater distance had been walked.

---

#### 12.3.2.3: Summary:

The second aim of this programme of research was to investigate the effects of TENS on measures of pain and walking performance in patients with IC. HF-TENS was shown to have a hypoalgesic effect on induced ischaemic pain in the lower limb of healthy volunteers. As a novel and untested intervention for IC pain, TENS applied to the lower limb of patients with IC was found to increase treadmill walking performance. However, despite increasing walking performance in patients with IC, TENS was not found to reduce overall pain intensity. This suggests that pain is a central determinant of walking performance in patients with IC. Again, by addressing this research aim, unique and novel contributions have been made to research and clinical practice.

---

#### 12.3.3: Clinical implications of the present findings:

The clinical implications of the current programme of work are limited due to the nature of the studies completed. Nevertheless, there are a number of important conclusions worthy of discussion. The pain experience of IC was found to be characterised by specific adjectives included in the MPQ. TENS was found to reduce the intensity of laboratory ischaemic pain and increase walking distance in patients with clinical lower limb ischaemic pain. These

findings warrant further investigation which could lead to clinical implications for the management of PAD and IC.

#### 12.3.3.1: Assessment and interventions that address the psychosocial aspects of PAD and IC:

---

With the aim of exploring the nature and qualities of IC pain, the relationships between baseline variables and treadmill walking distance were analysed. The significant relationships between psychosocial measures of pain (PSEQ) and treadmill measures (FCD and ACD), and the lack of relationships between treadmill measures and physiological variables (ABPI and BMI) suggest that the psychological aspects of pain are significantly associated with walking performance in this sample of patients with PAD and IC. The small sample size of the study means that these findings might not be representative of the population although the concept is worth further investigation. Previous studies have highlighted the role of general psychological and psychosocial factors in PAD and IC (Smolderen et al 2008; Garnefski et al 2009) but none have investigated the specific effect of pain-related psychological variables. Parr et al (2008) also found a lack of relationships between physiological measures and walking performance. If proven to exist, the relationships between psychological variables related to pain (i.e. pain self-efficacy) and walking performance could be a focus for effective clinical intervention. In other chronic pain syndromes, increased positive pain self-efficacy beliefs have been shown to relate to improvements in physical functioning and social participation, independent of pain intensity or disease severity (Turner et al 2005; Wong et al 2010). Currently, there are no reports of similar interventions for patients with PAD and IC. If the relationship between pain self-efficacy and walking distance in patients with IC is proven, interventions that target these beliefs may be an important clinical implication.

The qualitative follow-up study that examined the experience of using TENS at home for IC uncovered some key common themes of living with PAD and IC and using TENS at home for pain relief. Similar to previous studies that have examined the qualitative experience of living with PAD and IC (Gibson and Kenrick 1998; Wann-Hansson et al 2005, 2008; Egberg et

al 2012), frustration was found to be a core component of the experience with lack of knowledge and understanding of the disease and prognosis. This repetition of findings strengthens the level of evidence and reinforces the need for healthcare practitioners involved in PAD to engage with these issues and address them.

In fact, methods to address these identified issues have already been developed. Lauret et al (2012) reported on a national integrated care network that has been developed in the Netherlands for patients with PAD and IC. This network involves modifying the care of patients with PAD around a chronic care model that includes integrated working of all healthcare practitioners, patient education and coordinated supervised exercise. There has been no evaluation of its success as yet but it seems to address some of the issues highlighted by the current study.

#### 12.3.3.2: The mSETT as a method of inducing ischaemic pain in the lower limb of healthy volunteers and as a pre-clinical model of IC pain:

---

One major outcome of this body of work is the development of the mSETT method of inducing ischaemic pain in the lower limb of healthy volunteers. The mSETT has been shown to safely and reliably induce pain over two occasions (Chapter 7). It has also been shown to work as a method of inducing pain for the study of an intervention (Chapter 8) and the sensory components of the pain induced were found to be similar to that experienced in clinical IC pain (Chapter 10). Further examination of the reliability over longer periods, with a more heterogeneous sample and investigation of the inter-rater reliability are required prior to its acceptance as a reliable method for inducing lower limb ischaemic pain. If shown to be robust under further examination, the development of the mSETT may have clinical implications as a novel method of inducing pain that closely reflects clinical pain experience in the lower limb of healthy volunteers.

As a pre-clinical model of IC pain, the mSETT could be used to investigate the mechanisms of ischaemic pain in the lower limb. As discussed in Chapter 2, the mechanisms that lead to IC pain are not fully understood. The mSETT provides an opportunity to study the mechanisms

of pain on a model that induces ischaemia and produces pain with a stimulus shown to be similar to clinical IC. The mSETT method also provides an opportunity to investigate the effects of lower limb ischaemic pain on psychological and physical function. Experimental pain models are often used to investigate the effect of pain on certain psychological and physiological variables. The mSETT could be used to aid further understanding of the effects of pain, especially on lower limb function. Lastly, in the same way as it has been employed in the current programme of research, the mSETT may be useful for the investigation of interventions for pain. There are a number of current, valid and reliable methods with which to induce experimental pain. However, the mSETT is unique in area of pain induction (lower limb). It is also special in its ability, similar to the upper limb SETT, to allow the study of pain over a prolonged time period (pain threshold to tolerance).

These functions are primarily in the 'experimental pain' realm and are thus not strictly speaking 'clinical implications'. Nevertheless, further understanding of the mechanisms of ischaemic pain may help to inform clinical studies on intervention and the successful pre-clinical testing of interventions will influence clinical research and practice.

#### 12.3.3.3: Further evidence of the hypoalgesic effects of TENS and a possible new application in IC pain:

---

Systematic reviews of TENS for clinical pain syndromes are often limited by the methodological quality of the original research. Commonly, issues concern the lack of randomisation, blinding and the parameters chosen for TENS application (Brosseau et al 2003; Khadilkar et al 2008; Walsh et al 2009). The findings of this research may have clinical implications in this regard. Segmental delivery of HF-TENS with parameters set at 120Hz, 200µs and patient determined intensity of 'strong but comfortable' has been shown within this body of work to be effective at reducing experimental pain intensity and increasing walking distance of patients in pain. These findings align with those from other studies on experimental pain. In high quality studies on upper limb ischaemic pain, Walsh et al (1995a) and Chen and Johnson (2011) demonstrated hypoalgesic effects of HF-TENS delivered at 80-

110Hz, 200 or 287 $\mu$ s and 'strong but comfortable' intensity. These settings may serve as a good starting point from which to explore the hypoalgesic effects of TENS.

Prior to the inception of this programme of research, there was no published literature regarding hypoalgesic interventions specifically tested on IC pain. The results of this series of studies have demonstrated the efficacy of TENS in increasing treadmill walking performance in a small sample of patients with IC.

---

#### 12.3.4: Limitations of the studies included in this thesis:

---

This programme of research contributes a number of novel techniques and findings. Nevertheless, there are also a number of limitations that can be identified in the thesis. One of the most fundamental aspects common to both trials was incomplete blinding. In the laboratory study, only the participants were blinded to the intervention. This may have introduced bias to the experiment and resulted in overestimation of effect (Schulz et al 1995). Due to the nature of the application of TENS, achieving double blinding is challenging. As participants are asked to select their own subjective intensity level, an additional researcher is required to provide these instructions and answer any questions. In the current study, this was not feasible and it was decided that single blinding was sufficient. In an attempt to reduce the effect of this bias, the analysis of the data was conducted blind. An independent statistician coded the data so that the participant number and group were not known during analysis.

The issue of blinding was also present in the clinical study. In this case, as a second researcher was present for safety reasons, double blinding was possible. The second researcher collected all data during the testing procedure, and the TENS was applied and adjusted by the participant with help from the primary researcher. This reduced the possibility of bias in the results and reduced the chance of a Type 1 error.

One aspect of the clinical study that can be viewed as a limitation is the lack of a no-TENS control group. By neglecting to include a no-TENS condition it is impossible to quantify the

effect of 'intervention' or the placebo effect of TENS. This is an important and contentious ethical issue. It has been proposed that part of the beneficial effect of TENS is the sense of control and the perception of an 'intervention' experienced by patients when applying the device (Price et al 2008). Without a no-TENS group this effect cannot be quantified and thus the true overall effect of TENS could be underestimated i.e. increasing the possibility of a Type 2 error. The clinical study described within this thesis was designed as a proof-of-concept, MRC phase IIa trial and thus a pragmatic, clinical approach was assumed. When investigating the effects of TENS with the aim of evaluating demonstrable, physiological outcomes, TENS must demonstrate efficacy above placebo and thus the study design is sufficient. Future studies should include a no-TENS control to allow investigation of the placebo response to TENS in PAD and IC.

For the qualitative focus group study, the main limitation was the fact that the participants were not naïve to TENS and the research programme. As participants were recruited from the original study population, their decision to volunteer may have been affected by their experience of TENS during treadmill walking. This may have resulted in only those who had a favourable attitude towards TENS being included in the follow-up study, as those who had a negative experience would be less willing to use it at home for a further month. Also, their opinions of TENS may have been influenced by the general discussions and information given during the first study. Again, from a pragmatic, clinical viewpoint, it is likely that only patients who are open to the use of TENS will be provided with a device as an intervention. Also a device would normally only be provided after a trial period in which the patient would be encouraged to try it out and only after which they would decide whether to use it at home (Charlton 2005). Therefore this method of participant selection could be seen as sufficient.

Nevertheless, it is important in future investigations into the use of TENS at home for PAD and IC that different sampling methods are employed. Purposive sampling could be used and it would allow investigators to examine the effects and experience of TENS use in

participants specifically chosen for their diverse characteristics and attitude towards TENS as an intervention.

---

#### 12.3.5: Future Directions:

---

Analyses of the findings of this project indicate that further research is required to fully address the research questions identified. The direction of this research and specific research questions will now be discussed in turn relating to the specific chapter and studies from which they arise.

##### 12.3.5.1: Further laboratory investigations of mSETT-induced pain and the effects of TENS:

---

The findings discussed in Chapters 7 and 10 represent the first in-depth investigation of lower limb induced ischaemic pain. The limitations of these studies have been discussed (section 12.3.4) and it is clear that further investigation is required to comprehensively validate the mSETT as a pre-clinical model of IC pain. Key objectives of this research would be to 1) investigate the test-retest reliability of the mSETT over more than two occasions in a larger sample; 2) examine the inter-rater reliability of the mSETT; and 3) investigate if through manipulation of the mSETT parameters a pain experience can be induced that more closely reflects clinical IC pain. If achieved, the refined mSETT procedure could then be implemented as a robust pre-clinical model of IC pain and as a reliable method of inducing experimental pain in the lower limb of healthy volunteers.

In Chapter 8, the effects of HF-TENS on lower limb induced ischaemic pain were investigated. Systematic review evidence has shown that further investigation of TENS for ischaemic pain is required and has also identified the high quality methods required to achieve the appropriate level of evidence (Chapter 5) (Chen and Johnson 2011). Due to ethical and feasibility considerations, it was not possible to employ these methods in the current study. Future investigation is required to examine the effects of TENS on mSETT-induced pain in a double blind, repeated measures trial with the appropriate number of participants. This type of study would also allow for investigation of the optimal settings of

TENS (frequency, intensity, electrode placement) for reducing lower limb ischaemic pain. Such an investigation would not just allow for the investigation of the neurophysiological mechanisms of TENS but it could also inform the study of TENS for IC pain.

This model of laboratory pain may also provide a further opportunity to examine the relationships between psychological variables and the response to TENS. As reported in Chapter 9, significant relationships were found between patient controlled TENS intensity and pain self-efficacy. Currently no published literature could be found that investigates the effects of psychosocial variables on the efficacy of TENS. Future studies should include baseline measures of psychosocial variables when investigating the effects of TENS on experimental pain so that any relationships can be explored.

#### 12.3.5.2: Further clinical investigation of IC pain and the effects of TENS:

The design and findings of the clinical study of TENS for IC pain naturally lead to further investigation. As a proof-of-concept trial it was proposed that TENS could be effective at reducing pain and increasing walking distance in patients with IC. As the findings were positive and no adverse events were reported, the next step is to complete a phase IIb trial. This involves investigating the intervention in a larger group of participants and using different dosages of TENS with the aim of elucidating methodology for a phase III trial (e.g. decisions on outcomes, endpoints and randomisation). In the current situation this would involve examining different TENS parameters in a repeated measures design, and including a no-TENS control condition. It would also investigate additional methods for recording outcomes e.g. NRS throughout the treadmill test, SF-MPQ rather than MPQ and laser Doppler measurement of local tissue blood flow to examine the local physiological effects of TENS.

In addition to this more robust examination of the effects of TENS, the findings of the current study indicate the need for further investigation into the predictors of walking performance in patients with IC. This could be achieved within the context of the study described above but it may be more suited to a separate, larger scale investigation. A multi-



centre prospective study that investigates physiological and psychological variables and their relationships with physical function and quality of life in patients with PAD and IC could help to address some of the unanswered questions.

Exploring the subjective descriptions of IC pain was one of the aims of this thesis. The method employed when obtaining these descriptions was to ask patients with IC to complete the MPQ as soon as they had completed a treadmill exercise test in which they walked to maximal pain. This situation is an unusual one for these patients and as such they might have been experiencing increased levels of anxiety. The perceived meaning of the situation influences pain experience, thus it may not be the most ideal time to record pain descriptions. Future investigations should aim to record pain descriptions of IC in a more normal situation e.g. at home via postal survey. Also, as the pain descriptions were collected from a small number of participants in a certain geographical area the descriptions may not be generalisable to the wider IC population. To improve the generalisability, it is important to gather pain descriptions across a number of sites and from a larger sample of patients.

In the follow-up study, the experience of using TENS at home for IC was examined along with the general experience of living with PAD and IC (Chapter 11). The study was designed as a pragmatic qualitative investigation and as such the conclusions are limited to informing more robust investigation by identifying initial limitations in the methodology. Future research should therefore address these limitations and investigate the lived experience of using TENS at home for IC. As mentioned above, the sample studied is not necessarily representative of the wider IC population. Further qualitative investigation of TENS for IC should aim to address this as much as possible. Also, further research should aim to increase the depth of investigation and thus the conclusions drawn. For example, the length of the trial period of TENS could be increased. Some of the participants in the current study expressed a desire to try TENS for a longer period of time as they felt they couldn't decide after only 4 weeks of use. In addition, any physiological or behavioural changes that occur in this population whilst using TENS should be measured. For example, this could include measuring physiological markers of cardiovascular health, using physical activity monitors to

examine any change in activity whilst using TENS, or investigation of the effect of TENS use on participation in exercise therapy.

Other important themes identified in the qualitative study were patients' knowledge and understanding and the need for community-based support that encourages patients with PAD and IC to increase their level of activity. Currently there is no published literature examining the effect of educational strategies or community support interventions for patients with IC. This presents an opportunity for further research. Evaluation of the current state of the clinical delivery and development and implementation of such interventions could be beneficial for this population.

#### 12.4: CONCLUSION:

---

Peripheral Arterial Disease (PAD) causes significant reductions in physical and psychological function, resulting in a decrease in quality of life. PAD is a manifestation of more generalised atherosclerosis and only 20-30% of patients with PAD die of non-cardiovascular causes compared to approximately 75% in the general population (AHA 2012).

Management of PAD is focussed on risk factor reduction and exercise therapy, both of which have been shown to be effective. A problem for clinicians is that patients often have poor adherence to exercise. A major barrier for exercise in patients with PAD is Intermittent Claudication (IC).

IC, the cardinal symptom of PAD, is independently associated with increased levels of functional disability, psychological distress and increased risk of morbidity. Currently, the pain experience associated with IC is not fully understood and despite its highlighted consequences, there are no interventions recommended for IC pain.

IC pain is therefore an important area that requires investigation. An improved understanding of the pain experience could help clinicians manage this chronic pain condition. Interventions that reduce the burden of IC could help to encourage adherence to

exercise therapy and thus reduce the risk of patients progressing to more serious cardiovascular disease.

Transcutaneous Electrical Nerve Stimulation (TENS) is a safe, non-pharmacological and cheap method of providing non-invasive pain relief and may be useful for patients with PAD and IC. It has been shown to be effective in reducing pain and increasing function in chronic pain conditions but it has not been tested for IC pain.

This research programme has examined IC pain and investigated the effects of TENS on measures of pain and walking performance. This was achieved by first developing a method of inducing ischaemic pain in the lower limb of healthy volunteers. HF-TENS was found to elicit hypoalgesic effects on this induced lower limb laboratory ischaemic pain.

Both HF and LF-TENS were found to increase treadmill walking performance in patients with IC. Descriptions of laboratory and clinical lower limb ischaemic pain were recorded and compared; indicating that pain induced by the mSETT method is comparable in quality to clinical IC pain.

The experience of living with PAD and IC and using TENS for daily life was also explored. The experience of living with PAD and IC was characterised by feelings of frustration and the experience of using TENS at home by feelings of benefit yet disappointment.

The outcomes of this series of linked investigations is that the pain experience of IC is unique and complex and that TENS may prove to be a useful adjunctive intervention for walking performance in patients with IC. Further research should aim to replicate these findings in larger populations whilst employing more robust methods.

## CHAPTER 13: REFERENCES:

---

- Abelson, K., Langley, G.B., Sheppard, H., Vlieg, M., Wigley, R.D. 1983. Transcutaneous electrical nerve stimulation in rheumatoid arthritis. *New Zealand Medical Journal*. 96; pp 156–158
- Abramson, L.Y., Seligman, M.E.P., Teasdale, J.D. 1978. Learned helplessness in humans: critique and reformulation. *Journal of Abnormal Psychology*. 87(1); pp 49–74
- Alcadipani, R. Hodgson, D. 2009. By any means necessary? Ethnographic access, ethics and the critical researcher. *Tamara Journal for Critical Organization Inquiry*. 7(4); pp. 127-146
- Allan, G. 2003. A critique of using grounded theory as a research method. *Electronic Journal of Business Research Methods*. 2(1); pp. 1–10
- Allsop, P., Cheetham, M., Brooks, S., Hall, G.M. and Williams, C. 1990. Continuous intramuscular pH measurement during the recovery from brief, maximal exercise in man. *European Journal of Applied Physiology and Occupational Physiology*. 59(6); pp 465–470
- Almahameed, A. and Bhatt, D. L. 2006. Contemporary management of peripheral arterial disease: III. Endovascular and surgical management. *Cleveland Clinic Journal of Medicine*. 73(Suppl 4); pp S45
- Amanzio, M., and Benedetti, F. 1999. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning activated specific subsystems. *The Journal of Neuroscience*. 19(1); pp 484-494
- Amanzio, M., Pollo, A., Maggi, G., Benedetti, F. 2001. Response variability to analgesics: a role for non-specific activation of endogenous opioids. *Pain*. 90; pp 205-215
- American Heart Association (AHA) 2012. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation*. 125(1); pp e2–e220
- American Physical Therapy Association (APTA) 2001. Guide to physical therapist practice, 2<sup>nd</sup> Ed. *Physical Therapy*. 81; pp 9-744
- Andersson, S.A. 1979, Pain control by sensory stimulation. In *Advances in Pain Research and Therapy*. Eds. J.J. Bonica, J.C. Liebeskind & D.G. Albe-Fessard, Raven Press, New York, pp 569-585
- Anthonisen, N.R., Skeans, M.A., Wise, R.A., Manfreda, J., Kanner, R.E., Connett, J.E. 2005. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Annals of Internal Medicine*. 142(4); pp 233-239

- Aquarius, A.E., Denollet, J., Hamming, J.F., De Vries, J. 2005. Role of disease status and type-D personality in outcomes in patients with peripheral arterial disease. *American Journal of Cardiology*. 96; pp 996-1001
- Aquarius, A.E., De Vries, J., Van Berge Henegouwen, D.P., Hamming, J.F. 2006. Clinical indicators and psychological aspects in peripheral arterial disease. *Archives of Surgery*. 141; pp 161-166
- Asghari, A. and Nicholas, M.K. 2001. Pain self-efficacy beliefs and pain behaviour: a prospective study. *Pain*. 94(1); pp 85–100
- Asmundson, G.J.G., Vlaeyen, J.W.S., Crombez, G. 2004. *Understanding and Treating Fear of Pain*. Oxford University Press, Oxford, UK
- Antithrombotic Trialists' Collaboration (ATC) 2002. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients. *British Medical Journal*. 324(7329); pp 71–86
- Atkinson, G. and Nevill, A.M. 1998. Statistical methods for assessing measurement error (reliability) in variables relevant to sports medicine. *Sports Medicine*. 26(4); pp 217-238
- Autton, N. 1986. *Pain: an exploration*. London, Longman and Todd.
- Bandura, A. 2012. On the functional properties of perceived self-efficacy revisited. *Journal of Management*. 38(1); pp 9-44
- Bandura, A., Barbaranelli, C., Capara, G.V., Pastorelli, C. 2001. Self-efficacy beliefs as shapers of children's aspirations and career trajectories. *Child Development*. 72; pp 187-206
- Bandura, A. 1994. Self-efficacy. In V. S. Ramachaudran (Ed.), *Encyclopedia of human behaviour*. Vol. 4; pp 71-81. New York: Academic Press. (Reprinted in H. Friedman [Ed.], *Encyclopedia of mental health*. San Diego: Academic Press, 1998).
- Barbour, R. 2008. *Introducing Qualitative Research: A Student Guide to the Craft of Doing Qualitative Research*. London, UK: Sage Publications Ltd.
- Barlas, P. and Lundeborg, T. 2006. Transcutaneous electrical nerve stimulation and acupuncture. In: McMahon, S.B. Koltzenburg, M. Eds. *Wall and Melzack's Textbook of Pain*. 5<sup>th</sup> Ed. Edinburgh. Elsevier Churchill Livingstone.
- Bartelink, M.-L., Stoffers, H.E.J.H., Biesheuvel, C.J., Hoes, A.W. 2004. Walking exercise in patients with intermittent claudication. Experience in routine clinical practice. *British Journal of General Practice*. 54; pp 196–200

Becker, N., Thomsen, A., Olsen, A., Sjøgren, P., Bech, P., Eriksen, J. 1997. Pain epidemiology and health related quality of life in chronic non-malignant pain patients referred to a Danish multidisciplinary pain center. *Pain*. 73; pp 393-400

Beckitt, T.A., Day, J., Morgan, M., Lamont, P.M. 2012. Skeletal muscle adaptation in response to supervised exercise training for intermittent claudication. *European Journal of Vascular and Endovascular Surgery*. 44(3); pp 313–317

Belch, J.F.J., Topol, E.J., Agnelli, G., Bertrand, M., Califf, R.M., Clement, D.L., Creager, M.A., Easton, J.D. Gavin III, J.R. Greenland, P. Hankey, G. Hanrath, P. Hirsch, A.T. Meyer, J. Smith, S.C. Sullivan, F., Weber, M.A. 2003. Critical issues in peripheral arterial disease detection and management: A call to action. *Archives of Internal Medicine*. 163(8); pp 884–892

Belch, J., Stansby, G., Shearman, C., Brittenden, J., Dugdill, S., Fowkes, G., Jarvis, S., Mccann, T., Mimnagh, A., Monkman, D., Morrell, J. 2007. Peripheral arterial disease -- a cardiovascular time bomb. *The British Journal of Diabetes & Vascular Disease* 7(5): pp 236–239.

Bendermacher, B.L.W., Willigendael, E.M., Teijink, J.A.W., Prins, M.H. 2006. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication (Review). *Cochrane Database for Systematic Reviews*. Issue 2. Art. No.: CD005263

Benedetti, F. 1996. The opposite effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia. *Pain*. 64; pp 535-543

Benner, P. (Ed.). 1994. *Interpretive phenomenology: Embodiment, caring and ethics in health and illness*. Thousand Oaks, CA: Sage.

Berg, B.L. 2009. *Qualitative research methods for the social sciences*. 7<sup>th</sup> ed. Pearson, London.

British Heart Foundation (BHF) 2008. *Coronary Heart Disease Statistics Fact Sheet 2008/2009*. British Heart Foundation, London.

Bijur, P.E., Latimer, C.T., Gallagher, E.J. 2003. Validation of a verbally administered numerical rating scale of acute pain for use in the emergency department. *Academic Emergency Medicine*. 10(4); pp 390–392

Bjordal, J.M., Johnson, M.I., Ljunggreen, A.E. 2003. Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain. *European Journal of Pain*. 7(2); pp 181-188

Bjordal, J.M., Johnson, M.I., Lopes-Martins, R.A., Bogen, B., Chow, R., Ljunggren, A.E. 2007. Short-term efficacy of physical interventions in osteoarthritis knee pain. A systematic review

and meta-analysis of randomised placebo-controlled trials. *BMC Musculoskeletal Disorders*. 22; pp 8-51

Bolton, J.E. and Wilkinson, R.C. 1998. Responsiveness of pain scales: a comparison of three pain intensity measures in chiropractic patients. *Journal of Manipulative and Physiological Therapeutics*. 21; pp 1-7

Bonaa, K., Njolstad, I., Ueland, P., Schirmer, H., Tverdal, A., Steigen, T. 2006. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *New England Journal of Medicine*. 354; pp 1578-1588

Boothby, J.L., Thorn, B.E., Stroud, M.W., Jensen, M.P. 1999. Coping with pain. In R.J. Gatchel & D.C. Turk (Eds.), *Psychosocial factors in pain: Critical perspectives* (pp 343-359). New York: Guilford Press

Braun, V., Clarke, V. 2006. Using thematic analysis in psychology. *Qualitative Research in Psychology*. 3(2); pp 77–101

Breek, J.C., Hamming, J.F., De Vries, J., Aquarius, A.E.A.M., van Berge Henegouwen, D.P., 2001. Quality of life in patients with intermittent claudication using the World Health Organisation (WHO) questionnaire. *European Journal of Vascular and Endovascular Surgery*. 21; pp 118–122

Brekke, M., Hjortdahl, P., Kvien, T.K. 2003. Changes in self-efficacy and health status over 5 years: A longitudinal observational study of 306 patients with rheumatoid arthritis. *Arthritis & Rheumatism*. 49(3); pp 342–348

Brevetti, G., Diehm, C., Lambert, D. 1999. European multicenter study on Propionyl-Lcarnitine in intermittent claudication. *Journal of American College of Cardiology*. 34; pp 1618-1624

Briggs, M. and Closs, J.S. 1999. A descriptive study of the use of visual analogue scales and verbal rating scales for the assessment of postoperative pain in orthopedic patients. *Journal of Pain and Symptom Management*. 18(6); pp 438–446

Broderick, J.E., Schwartz, J.E., Vikingstad, G., Pribbernow, M., Grossman, S., Stone, A.A. 2008. The accuracy of pain and fatigue items across different reporting periods. *Pain*. 139(1); pp 146–157

Brooks, J. and Tracey, I. 2005. From nociception to pain perception: imaging the spinal and supraspinal pathways. *Journal of Anatomy*. 207(1); pp 19–33

Brosseau, L., Yonge, K., Welch, V., Marchand, S., Judd, M.G., Wells, G., Tugwell, P. 2003. Transcutaneous electrical nerve stimulation (TENS) for the treatment of rheumatoid arthritis in the hand. *Cochrane Database of Systematic Reviews*. Issue 2: CD004377

- Brown, L., Tabasam, G., Bjordal, J.M., Johnson, M.I. 2007, An investigation into the effect of electrode placement of transcutaneous electrical nerve stimulation (TENS) on experimentally induced ischemic pain in healthy human participants, *Clinical Journal of Pain*. 23(9); pp 735-743
- Bruce, J., Poobalan, A.S., Smith, W.C.S., Chambers, W.A. 2004. Quantitative assessment of chronic postsurgical pain using the McGill Pain Questionnaire. *The Clinical Journal of Pain*. 20(2); pp 70-75
- Buckelew, S.P., Parker, J.C., Keefe, F.J., Deuser, W.E., Crews, T.M., Conway, R., Kay, D.R., Hewett, J.E. 1994. Self-efficacy and pain behavior among subjects with fibromyalgia. *Pain*. 59(3); pp 377-384
- Buer, N. and Linton, S.J. 2002. Fear-avoidance beliefs and catastrophizing: occurrence and risk factor in back pain and ADL in the general population. *Pain*. 99(3); pp 485-491
- Bulmer, A.C. and Coombes, J.S. 2004. Optimising Exercise Training in Peripheral Arterial Disease: Review. *Sports Medicine*. 34(14); pp 983-1003
- Burckhardt, C.S. 1984. The use of the McGill Pain Questionnaire in assessing arthritis pain. *Pain*. 19(3); pp 305-314
- Caelli, K. 2001. Engaging with Phenomenology: Is it more of a Challenge than it Needs to be? *Qualitative Health Research*. 11(2); pp. 273-281
- CAPRIE Steering Committee 1996. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *The Lancet*. 348(9038); pp 1329-1339
- Carman, T.L. and Fernandez, B.B. 2006. Contemporary management of peripheral arterial disease: II. Improving walking distance and quality of life. *Cleveland Clinic Journal of Medicine*. 73 (Suppl 4); pp S38
- Carragee, E.J., Alamin, T.F., Miller, J.L., Carragee, J.M. 2005. Discographic, MRI and psychosocial determinants of low back pain disability and remission: a prospective study in subjects with benign persistent back pain. *The Spine Journal*. 5(1); pp 24-35
- Carroll, D., Trainer, M., McQuay, H., Nye, B., Moore, A. 1996 Randomisation is important in studies with pain outcomes: systematic review of transcutaneous electrical nerve stimulation in acute postoperative pain. *British Journal of Anaesthesia*. 77; pp 798-803
- Carroll, D., Moore, R.A., McQuay, H.J., Fairman, F., Tramer, M., Leijon, G. 2000. Transcutaneous electrical nerve stimulation (TENS) for chronic pain. *Cochrane Database of Systematic Reviews* Issue 4: CD003222



Charlton, J. 2005. *Core Curriculum for Professional Education in Pain*. 3rd Ed. Seattle: IASP press pp 93-96

Chartered Society of Physiotherapy (CSP) 2006. *2006 Guidelines for the Clinical use of Electrophysical Agents*. Chartered Society of Physiotherapy. London.

Chen, A.C. and Treede, R.D. 1985. The McGill Pain Questionnaire in the assessment of phasic and tonic experimental pain: behavioral evaluation of the 'pain inhibiting pain' effect. *Pain*. 22(1); pp 67-79

Chen, C.C. and Johnson, M.I. 2010a. An Investigation Into the Hypoalgesic Effects of High- and Low-Frequency Transcutaneous Electrical Nerve Stimulation (TENS) on Experimentally-Induced Blunt Pressure Pain in Healthy Human Participants, *Journal of Pain*. 11(1); pp 53-61

Chen, C.C. and Johnson, M.I. 2010b. A comparison of transcutaneous electrical nerve stimulation (TENS) at 3 and 80 pulses per second on cold-pressor pain in healthy human participants. *Clinical Physiology and Functional Imaging*. 30(4); pp 260–268

Chen, C.C. and Johnson, M.I. 2011. Differential frequency effects of strong nonpainful transcutaneous electrical nerve stimulation on experimentally induced ischemic pain in healthy human participants. *Clinical Journal of Pain*. 27(5); pp 434-441

Chen, C.C., Tabasam, G., Johnson, M.I. 2008. Does the pulse frequency of transcutaneous electrical nerve stimulation (TENS) influence hypoalgesia? A systematic review of studies using experimental pain and healthy human participants, *Physiotherapy*. 94(1); pp 11-20

Chesterton, L.S., Foster, N.E., Wright, C.C., Baxter, G.D., Barlas, P. 2003. Effects of TENS frequency, intensity and stimulation site parameter manipulation on pressure pain thresholds in healthy human subjects, *Pain*. 106(1-2); pp 73-80

Chetter, I.C., Spark, J.I., Dolan, P., Scott, D.J.A., Kester, R.C., 1997. Quality of life analysis in patients with lower limb ischaemia: suggestions for European standardisation. *European Journal of Vascular and Endovascular Surgery*. 13; pp 597–604

Claydon, L.S., Chesterton, L.S., Barlas, P., Sim, J. 2011. Dose-specific effects of transcutaneous electrical nerve stimulation (TENS) on experimental pain: a systematic review. *The Clinical Journal of Pain*. 27(7); pp 635–647

Coghill, R., McHaffie, J., Yen, Y. 2003. Neural correlates of interindividual differences in the subjective experience of pain. In: *Proceedings of the National Academy of Science of the United States of America*. pp 8538-8542.

Cohen, J. 1988. *Statistical Power Analysis for the Behavioral Sciences* 2nd Ed. Hillsdale, NJ: Lawrence Earlbaum Associates

Collins, T., Lunos, S., Carlson, T., Henderson, K., Lightbourne, M., Nelson, B., Hodges, J. 2011. Effects of a home-based walking intervention on mobility and quality of life in people with diabetes and peripheral arterial disease: a randomized controlled trial. *Diabetes Care*. 34(10); pp 2174-2179

Collins, T.C., Lunos, S., Ahluwalia, J.S. 2010. Self-efficacy is associated with walking ability in persons with diabetes mellitus and peripheral arterial disease. *Vascular Medicine*. 15(3); pp. 189–195

Collins, E.G., Langbein, W.E., Orebaugh, C., Bammert, C., Hanson, K., Reda, D., 2005. Cardiovascular training effect associated with polestriding exercise in patients with peripheral arterial disease. *Journal of Cardiovascular Nursing*. 20; pp 177-185

Corbin, J.M. Strauss, A. 1990. Grounded theory research: Procedures, canons, and evaluative criteria. *Qualitative Sociology*. 13(1); pp 3–21

Costa, F., Sulur, P., Angel, M., Cavalcante, J., Haile, V., Christman, B. and Biaggioni, I. 1999. Intravascular source of adenosine during forearm ischemia in humans: implications for reactive hyperemia. *Hypertension*. 33(6); pp 1453–1457

Coughlin, P.A., Kent, P.J., Berridge, D.C., Scott, D.J.A., Kester, R.C. 2006. The PADHOC device is a better guide to the actual incapacity suffered by claudicants than the gold standard constant load treadmill test. *European Journal of Vascular & Endovascular Surgery*. 32(6); pp 651–656

Craig, C.L., Marshall, A.L., Sjostrom, M., Bauman, A.E., Booth, M.L., Ainsworth, B.E., Pratt, M., Ekelund, U., Yngve, A., Sallis, J.F., Oja, P. 2003. International physical activity questionnaire: 12-country reliability and validity. *Medicine and Science in Sports and Exercise*. 35(8); pp 1381-1395

Criqui, M.H. 2001. Peripheral arterial disease- epidemiological aspects. *Vascular Medicine*. 6(1 suppl); pp 3–7

Criqui, M.H., Fronek, A., Barrett-Connor, E., Klauber, M.R., Gabriel, S., Goodman, D. 1985. The prevalence of peripheral arterial disease in a defined population. *Circulation*. 71(3); pp 510-551

Croft, P., Blyth, F.M. van der Windt, D. 2010. Chapter 1: Chronic pain as a topic for epidemiology and public health. In Croft, P., Blyth, F.M., van der Windt, D. eds. *Chronic Pain Epidemiology from Aetiology to Public Health*. Oxford, Oxford University Press

Crombez, G., Eccleston, C., Van Damme, S., Vlaeyen, J.W.S., Karoly, P. 2012. Fear-avoidance model of chronic pain: the next generation. *The Clinical Journal of Pain*. 28(6); pp 475-483

Crombez, G., Vlaeyen, J.W.S., Heuts, P.H.T.G., Lysens, R. 1999. Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability. *Pain*. 80; pp 329-339

Cunningham, M.A., Swanson, V., O'Carroll, R.E., Holdsworth, R.J. 2011. Randomized clinical trial of a brief psychological intervention to increase walking in patients with intermittent claudication. *British Journal of Surgery*. 99(1); pp 49–56

Currie, I.C., Wilson, I.G., Baird, R.N., Lamont, P.M. 1995. Treatment of intermittent claudication: The impact on quality of life. *European Journal of Vascular and Endovascular Surgery*. 10; pp 356-361

D'Souza, J., Patel, N.N.B., Rucker, M., Townsend, E., Morris-Stiff, G., Magee, T.R., Galland, R.B., Lewis, M.H. 2008. Management of cardiovascular risk factors by primary care physicians in patients with peripheral arterial disease. *The Surgeon*. 6(3); pp 144–147

de Backer, G., Ambrosioni, E., Borch-Johnsen, K., Brotons, C., Cifkova, R., Dallongeville, J., Ebrahim, S., Faergeman, O., Graham, I., Mancia, G., Cats, V.M., Orth-Gomér, K., Perk, J., Pyörälä, K., Rodicio, J.L., Sans, S., Sansoy, V., Sechtem, U., Silber, S., Thomsen, T., Wood, D. 2003. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *European Heart Journal*. 24(17); pp 1601-1610

de Backer, T., Vander Stichele, R., Leheret, P., Van Bortel, L. 2009. Naftidrofuryl for intermittent claudication: meta-analysis based on individual patient data. *British Medical Journal*. 338; pp. b603–b603

Defrin, R., Ariel, E., Peretz, C. 2005. Segmental noxious versus innocuous electrical stimulation for chronic pain relief and the effect of fading sensation during treatment. *Pain*. 115(1-2); pp 152-160

DeLoach, L.J., Higgins, M.S., Caplan, A.B., Stiff, J.L. 1998. The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. *Anesthesia & Analgesia*. 86(1); pp 102-106

Dersh, J., Gatchel, R.J., Mayer, T., Polatin, P., Temple, O.R. 2006. Prevalence of psychiatric disorders in patients with chronic disabling occupational spinal disorders. *Spine*. 31(10); pp. 1156–1162

DeSantana, J.M., Da Silva, L.F.S., De Resende, M.A., Sluka, K.A. 2009. Transcutaneous electrical nerve stimulation at both high and low frequencies activates ventrolateral periaqueductal grey to decrease mechanical hyperalgesia in arthritic rats. *Neuroscience*. 163(4); pp 1233-1241

DeSantana, J.M., Walsh, D.M., Vance, C., Rakel, B.A., Sluka, K.A. 2008. Effectiveness of transcutaneous electrical nerve stimulation for treatment of hyperalgesia and pain. *Current Rheumatology Reports*. 10(6); pp 492-499

Dobratz, M.C. 2008. Word choices of advanced cancer patients: frequency of nociceptive and neuropathic pain. *American Journal of Hospice and Palliative Medicine*. 25(6); pp 469–475

Dormandy, J.A., Charbonnel, B., Eckland, D.J., Erdmann, E., Massi-Benedetti, M., Moules, I.K. 2005. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 366(9493); pp 1279-1289

Downe-Wamboldt, B. 1992. Content analysis: method, applications and issues. *Health Care for Women International*. 13; pp 313–321

Dubuisson, D. and Melzack, R. 1976. Classification of clinical pain descriptions by multiple group discriminant analysis. *Experimental Neurology*. 51; pp 480-487

Dudgeon, D., Raubertas, R.F., Rosenthal, S.N. 1993. The short-form McGill Pain Questionnaire in chronic cancer pain. *Journal of Pain and Symptom Management*. 8(4); pp. 191-195

Dudgeon, B.J., Ehde, D.M., Cardenas, D.D., Engel, J.M., Hoffman, A.J., Jensen, M.P. 2005. Describing pain with physical disability: Narrative interviews and the McGill Pain Questionnaire. *Archives of Physical Medicine and Rehabilitation*. 86(1); pp 109-115

Dusseldorp, E., van Elderen, T., Maes, S., Meulman, J., Kraaij, V. 1999. A Meta-Analysis of Psychoeducational Programs for Coronary Heart Disease Patients. *Health Psychology*. 18(5); pp 506–519

Dworkin, R.H., Turk, D.C., Reveck, D.A., Harding, G., Coyne, K.S., Peirce-Sandner, S., Bhagwat, D., Burke, L.B., Cowan, P., Farrar, J.T., Hertz, S., Max, M.B., Rappaport, B.A., Melzack, R. 2009. Development and initial validation of an expanded and revised version of the Short-form McGill Pain Questionnaire (SF-MPQ-2). *Pain*. 144; pp 35-42

Eccles, J.S. and Wigfield, A. 2002. Motivational beliefs, values and goals. *Annual Reviews in Psychology*. 53; pp 109-132

Eccleston, C. and Crombez, G. 1999. Pain demands attention: A cognitive-affective model of the interruptive function of pain. *Psychological Bulletin*. 125(3); pp 356-366

Edwards, R.R., Calahan, C., Mensing, G., Smith, M., Haythornthwaite, J. 2011. Pain, catastrophizing, and depression in the rheumatic diseases. *Nature Reviews Rheumatology*. 7; pp 216–24

Egberg, L., Andreassen, S., Mattiasson, AC. 2012. Experiences of living with intermittent claudication. *Journal of Vascular Nursing*. 30; pp 5-10

Eliasziw, M., Young, S.L., Woodbury, M.G., Fryday-Field, K. 1994. Statistical methodology for the concurrent assessment of interrater and intrarater reliability using goniometric measurements as an example. *Physical Therapy*. 74(8); pp 777-788

Eriksson, M. 2006. Antonovsky's sense of coherence scale and the relation with health: a systematic review. *Journal of Epidemiology & Community Health*. 60(5); pp. 376–381

Eriksson, M.B., Sjolund, B.H., Niclzc, S. 1979. Long-term results of peripheral conditioning stimulation as an analgesic measure in chronic pain. *Pain*. 6; pp 335-347

Eriksson, M.B.E., Rosen, I., Sjolund, B. 1985. Thermal sensitivity in healthy subjects is decreased by a central mechanism after TNS. *Pain*. 22(3); pp 235-242

Eriksson, M.B.E. and Sjolund, B. 1976. Acupuncture-like electroanalgesia in TNS resistant chronic pain. In: Zotterman, Y. (Ed). *Sensory Functions of the Skin*. Oxford/New York; Pergamon Press pp 575-581

European Society of Hypertension-European Society of Cardiology (ESH/ESC) 2003. European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *Journal of Hypertension*. 21(6); pp 1011-1053

Falcone, R.A., Hirsch, A.T., Regensteiner, J.G., Treat-Jacobson, D., Williams, M.A., Hiatt, W.R., Stewart, K.J. 2003. Peripheral arterial disease rehabilitation. A review. *Journal of Cardiopulmonary Rehabilitation*. 23; pp 170-175

Farrar, J.T., Young, J.P., LaMoreaux, L., Werth, J.L., Poole, R.M. 2001. Clinical importance of changes in chronic pain intensity measured on an 11- point numerical pain rating scale. *Pain*. 94; pp 149–158

Fernandez, E. and Towery, S. 1997. A parsimonious set of verbal descriptors of pain sensation derived from the McGill Pain Questionnaire. *Pain*. 66(1); pp 31–37

Fishbain, D.A., Cutler, R., Rosomoff, H.L., Rosomoff, R.S. 1997. Chronic pain-associated depression: antecedent or consequence of chronic pain? A review. *The Clinical Journal of Pain*. 13(2); pp 116–137

Foster, N.E., Baxter, F., Walsh, D.M., Baxter, G.D., Allen J.M. 1996. Manipulation of transcutaneous electrical nerve stimulation variables has no effect on two models of experimental pain in humans. *Clinical Journal of Pain*. 12(4); pp 301-310

Francis, R.P., Marchant, P.R., Johnson, M.I. 2011. Comparison of post-treatment effects of conventional and acupuncture-like transcutaneous electrical nerve stimulation (TENS): A randomised placebo-controlled study using cold-induced pain and healthy human participants. *Physiotherapy Theory and Practice*. 27(8); pp 578-585

Frans, F.A., Bipat, S., Reekers, J.A., Legemate, D.A., Koelemay, M.J.W. 2011. Systematic review of exercise training or percutaneous transluminal angioplasty for intermittent claudication. *British Journal of Surgery*. 99(1); pp 16–28

Gagliese, L. and Melzack, R. 2003. Age-related differences in the qualities but not the intensity of chronic pain. *Pain*. 104(3); pp 597–608

Galea, M.N. and Bray, S.R. 2007. Determinants of walking exercise among individuals with intermittent claudication: does pain play a role? *Journal of Cardiopulmonary Rehabilitation and Prevention*. 27(2); pp 107–113

Galea, M.N., Bray, S.R., Martin Ginis, K.A. 2008. Barriers and facilitators for walking in individuals with intermittent claudication. *Journal of Aging and Physical Activity*. 16; pp 69-84

Galer, B.S., Gianas, A., Jensen, M.P. 2000. Painful diabetic polyneuropathy: epidemiology, pain description, and quality of life. *Diabetes Research and Clinical Practice*. 47(2); pp 123–128

Gandhi, R., Tsvetkov, D., Dhottar, H., Davey, J.R., Mahomed, N.N. 2010. Quantifying the pain experience in hip and knee osteoarthritis. *Pain research & management : the journal of the Canadian Pain Society*. 15(4); pp 224–228

Garcia L.A. 2006. Epidemiology and Pathophysiology of Lower Extremity Peripheral Arterial Disease. *Journal of Endovascular Therapy*. 13(Suppl II); pp II-3-II-9.

Gardner, A.W., Skinner, J.S., Cantwell, B.W., Smith, L.K. 1991. Progressive vs single-stage treadmill tests for evaluation of claudication. *Medicine and Science in Sports and Exercise*. 23(4); pp 402-408

Gardner, A.W. and Poehlman, E.T. 1995. Exercise rehabilitation programs for the treatment of claudication pain: a meta-analysis. *JAMA*. 274; pp 975-980

Gardner, A.W.P. and Afaq, Z.M. 2008. Management of lower extremity peripheral arterial disease. [Review]. *Journal of Cardiopulmonary Rehabilitation & Prevention*. 28(6); pp 349-357

Gardner, A.W., Parker, D.E., Webb, N., Montgomery, P.S., Scott, K.J., Blevins, S.M. 2008. Calf muscle hemoglobin oxygen saturation characteristics and exercise performance in patients with intermittent claudication. *Journal of Vascular Surgery*. 48(3); pp 644–649

Gardner, A.W.P., Katzel, L.I.M., Sorkin, J.D.M., Bradham, D.D.D., Hochberg, M.C.M., Flinn, W.R.M., Goldberg, A.P.M. 2001. Exercise rehabilitation improves functional outcomes and peripheral circulation in patients with intermittent claudication: a randomized controlled trial. *Journal of the American Geriatrics Society*. 49(6); pp 755-762

Gardner, A.W., Montgomery, P.S., Blevins, S.M., Parker, D.E. 2010. Gender and ethnic differences in arterial compliance in patients with intermittent claudication. *Journal of Vascular Surgery*. 51; pp 610-615

Garnefski, N., Grol, M., Kraaij, V., Hamming, J.F. 2009. Cognitive coping and goal adjustment in people with Peripheral Arterial Disease: Relationships with depressive symptoms. *Patient Education and Counseling*. 79; pp 132-137

Garrison, D.W. and Foreman, R.D. 1994. Decreased activity of spontaneous and noxiously evoked dorsal horn cells during transcutaneous electrical nerve stimulation (TENS). *Pain*. 58; pp 309-315

Gatchel, R.J., Peng, Y.B., Peters, M.L., Fuchs, P.N., Turk, D.C. 2007. The biopsychosocial approach to chronic pain: Scientific advances and future directions. *Psychological Bulletin*. 133(4); pp 581-624

Gazmararian, J.A., Williams, M.V., Peel, J., Baker, D.W. 2003. Health literacy and knowledge of chronic disease. *Patient Education and Counseling*. 51(3); pp 267-275

Geertz, C. 2001. Thick description: Toward an interpretive theory of culture. *The American Tradition in Qualitative Research*. 1; pp 298-320

Geisser, M.E., Haig, A.J., Theisen, M.E. 2000. Activity avoidance and function in persons with chronic back pain. *Journal of Occupational Rehabilitation*. 10(3); pp 215-227

Geisser, M.E., Robinson, M.E., Keefe, F.J., Weiner, M.L. 1994. Catastrophizing, depression and the sensory, affective and evaluative aspects of chronic pain. *Pain*. 59(1); pp 79-83

George, S.Z., Dannecker, E.A., Robinson, M.E. 2006. Fear of pain, not pain catastrophizing, predicts acute pain intensity, but neither factor predicts tolerance or blood pressure reactivity: An experimental investigation in pain-free individuals. *European Journal of Pain*. 10; pp 457-465

Gibson, J.M.E. and Kenrick, M. 1998. Pain and powerlessness: the experience of living with peripheral vascular disease. *Journal of Advanced Nursing*. 27(4); pp 737-745

Gil, K.M., Abrams, M.R., Phillips, G., Williams, D.A. 1992. Sickle cell disease pain: 2. Predicting health care use and activity level at 9-month follow-up. *Journal of Consulting and Clinical Psychology*. 60(2); pp 267-273

Gil, K.M., Thompson, R.J., Keith, B.R., Tota-Faucette, M., Noll, S., Kinney, T.R. 1993. Sickle cell disease pain in children and adolescents: change in pain frequency and coping strategies over time. *Journal of Pediatric Psychology*. 18(5); pp 621–637

Giorgi, A. 1992. Description versus interpretation: Competing alternative strategies for qualitative research. *Journal of Phenomenological Psychology*. 23(2); pp. 119–135

Giorgi, A. 2005. The Phenomenological Movement and Research in the Human Sciences. *Nursing Science Quarterly*. 18(1); pp 75–82

Giorgi, A. 2006. Difficulties encountered in the application of the phenomenological method in the social sciences. *Análise Psicológica*. 24(3); pp 353–361

Glaser, B.G. Strauss, A.L. 1967. The discovery of grounded theory: Strategies for qualitative research. Chicago: Aldine.

Gracely R.H. 2006. Studies of pain in human subjects. In: McMahon, S.B. Koltzenburg, M. Eds. *Wall and Melzack's Textbook of Pain*. 5<sup>th</sup> Ed. Edinburgh. Elsevier Churchill Livingstone.

Gracely, R.H., Geisser, M.E., Giesecke, T., Grant, M.A.B., Petzke, F., Williams, D.A., Clauw, D.J. 2004. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain*. 127(4); pp 835–843

Grafton, K.V., Foster, N.E., Wright, C.C. 2005. Test-retest reliability of the Short-form McGill Pain Questionnaire: assessment of intraclass correlation coefficients and limits of agreement in patients with osteoarthritis. *Clinical Journal of Pain*. 21; pp 73–82

Graham, C., Bond, S.S., Gerkovich, M.M., Cook, M.R. 1980. Use of the McGill pain questionnaire in the assessment of cancer pain: replicability and consistency. *Pain*. 8(3); pp 377–387

Granot, M. and Ferber, S.G. 2005. The roles of pain catastrophizing and anxiety in the prediction of postoperative pain intensity: a prospective study. *Clinical Journal of Pain*. 21(5); pp 439–445

Graven-Nielsen, T. and Arendt-Nielsen, A. 2008. Impact of clinical and experimental pain on muscle strength and activity. *Current Rheumatology Reports*. 10(6); pp 475-481

Graven-Nielsen, T., Segerdahl, M., Svensson P., Arendt-Nielsen L. 2001. Methods for induction and assessment of pain in humans with clinical and pharmacological examples. In: *Methods in pain research*. L. Kruger Ed. CRC Press, Boca Raton, pp 264–304

Graven-Nielsen, T., Jansson, Y., Sergerdahl, M., Kristensen, J.D., Mense, S., Arendt-Nielsen, L., Sollevi, A. 2003. Experimental pain by ischaemic contractions compared with pain by



intramuscular infusions of adenosine and hypertonic saline. *European Journal of Pain*. 7; pp 93-102

Grushka M. and Sessle B.J. 1984. Applicability of the McGill Pain Questionnaire to the differentiation of “toothache” pain. *Pain*. 19; pp 49-57

Gustin, S.M., Wilcox, S.L., Peck, C.C., Murray, G.M., Henderson, L.A. 2011. Similarity of suffering: equivalence of psychological and psychosocial factors in neuropathic and non-neuropathic orofacial pain patients. *Pain*. 152; pp 825-832

Hamza, M.A., White, P.F., Ahmed, H.E., Ghoname, E.A. 1999. Effect of the frequency of transcutaneous electrical nerve stimulation on the postoperative opioid analgesic requirement and recovery profile. *Anesthesiology*. 91; pp 1232-1238

Handwerker, H.O. and Kobal, G. 1993. Physiology of experimentally induced pain. *Physiology Review*. 73; pp 639–671

Hankey, G.J., Norman, P.E., Eikelboom, J.W. 2006. Medical treatment of Peripheral Arterial Disease. *Journal of the American Medical Association*. 295(5); pp 547-53

Hanmburg, N.H. and Balady, G.J. 2011. Exercise rehabilitation in peripheral artery disease: functional impact and mechanisms of benefits. *Circulation*. 123; pp 87-97

Harpuder, K. and Stein, I.D. 1943. Studies on the nature of pain arising from an ischemic limb: I. Clinico-experimental observations. *American Heart Journal*. 25(4); pp 429–437

Hawker, G.A., Mian, S., Kendzerska, T., French, M. 2011. Measures of adult pain: Visual Analog Scale for pain (VAS pain), Numeric Rating Scale for pain (NRS pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and measure of Intermittent And Constant Osteoarthritis Pain (ICOAP). *Arthritis Care & Research*. 63(S11); pp S240–S252

Heald C.L., Fowkes, F.G., Murray, G.D., Price, J.F. 2006. Ankle Brachial Index Collaboration. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: systematic review. *Atherosclerosis*. 189; pp 61–69

Heart Protection Study Collaborative Group (HPSCG) 2002. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 360(9326); pp 7-22

Hiatt, W.R. 2001. Medical treatment of peripheral arterial disease and claudication. *New England Journal of Medicine*. 344; pp 1608-1621

Hiatt, W.R., Hoag, S., Hamman, R.F. 1995. Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. *Circulation*. 91(5); pp 1472-1479

Hiatt, W.R., Regensteiner, J.G., Wolfel, E.E., Carry, M.R., Brass, E.P. 1996. Effect of exercise training on skeletal muscle histology and metabolism in peripheral arterial disease. *Journal of Applied Physiology*. 81(2); pp 780–788

Hiatt, W.R., Regensteiner, J.G., Creager, M.A., Hirsch, A.T., Cooke, J.P., Olin, J.W., Gorbunov, G.N., Isner, J., Lukjanov, Y.V., Tsitsiashvili, M.S., Zabelskaya, T.F., Amato, A. 2001. Propionyl-L-carnitine improves exercise performance and functional status in patients with claudication. *The American Journal of Medicine*. 110(8); pp 616–622

Hillsdon, M., Foster, C., Thorogood, M. 2005. Interventions for promoting physical activity. *Cochrane Database of Systematic Reviews*. 2005(1):CD003180.

Hirsch, A.T., Criqui, M.H., Treat-Jacobson, D., Regensteiner, J.G., Creager, M.A., Olin, J.W., Krook, S.H., Hunninghake, D.B., Comerota, A.J., Walsh, M.E. 2001. Peripheral arterial disease detection, awareness, and treatment in primary care. *Journal of the American Medical Association*. 286(11); pp 1317–1324

Hirsch, A.T., Haskal, Z.J., Hertzler, N.R., Bakal, C.W., Creager, M.A., Halperin, J.L., Hiratzka, L.F., Murphy, W.R.C., Olin, J.W., Puschett, J.B., Rosenfield, K.A., Sacks, D., Stanley, J.C., Taylor, L.M.Jr., White, C.J., White, J., White, R.A. 2005. ACC/AHA 2005 Practice Guidelines for the Management of Patients With Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic) A Collaborative Report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). *Circulation*. 113; pp e463-e465

Hirsh, A.T., George, S.Z., Bialosky, J.E., Robinson, M.E. 2008. Fear of pain, pain catastrophizing, and acute pain perception: relative prediction and timing of assessment. *The Journal of Pain*. 9(9); pp 806–812

Holroyd, K.A., Hoim, J.E., Keefe, F.J., Turner, J.A., Bradley, L.A., Murphy, W.D., Johnson, P., Anderson, K., Hinkle, A.L., O'Malley, W.B. 1992. A multi-center evaluation of the McGill Pain Questionnaire: results from more than 1700 chronic pain patients. *Pain*. 48; pp 301–311

Holtan, A. and Kongsgaard, U.E. 2009. The use of pain descriptors in cancer patients. *Journal of Pain and Symptom Management*. 38(2); pp 208–215

Hood, S.C., Moher, D., Barber, G.G. 1996. Management of intermittent claudication with pentoxifylline: meta-analysis of randomized controlled trials. *Canadian Medical Association Journal*. 155(8); pp 1053-1059

Hurlow, A., Bennett, M.I., Robb, K.A., Johnson, M.I., Simpson, K.H., Oxberry, S.G. 2012. Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults. *Cochrane Database of Systematic Reviews* Issue 3.

Izquierdo-Porrera, A.M., Gardner, A.W., Powell, C.C., Katzel, L.I. 2000. Effects of exercise rehabilitation on cardiovascular risk factors in older patients with peripheral arterial occlusive disease. *Journal of Vascular Surgery*. 31(4); pp 670–677

Jacobson, P. and Butler, R. 1996. Relation of cognitive coping and catastrophizing to acute pain and analgesic use following breast cancer surgery. *Journal of Behavioral Medicine*. 19; pp 17-29

Jacoby D. and Mohler E.R. 2004. Drug treatment of intermittent claudication. *Drugs*. 64(15); pp 1657-1670

Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J., McQuay, H.J. 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials*. 17(1); pp 1–12

Jenkinson, C., Carroll, D., Egerton, M., Frankland, T., McQuay, H., Nagle, C. 1995. Comparison of the sensitivity to change of long and short form pain measures. *Quality of Life Research*. 4(4); pp 353–357

Jensen, M.P., Karoly, P., Braver, S. 1986 the measurement of clinical pain intensity: a comparison of six methods. *Pain*. 27; pp 117-126

Jensen, M.P., Turner, J.A., Romano, J.M. 1994 what is the maximum number of levels needed in pain intensity measurement. *Pain*. 58; pp 387-392

Jerome, A., Holroyd, K.A., Theofanous, A.G., Pingel, J.D., Lake, A.E., Saper, J.R. 1988. Cluster headache pain vs. other vascular headache pain: differences revealed with two approaches to the McGill Pain Questionnaire. *Pain*. 34; pp 35-42

Johnson, M.I. 2001. Transcutaneous Electrical Nerve Stimulation (TENS) and TENS-like devices: do they provide pain relief? *Pain Reviews*. 8(3-4); pp 121–158

Johnson, M.I. 2002. Transcutaneous Electrical Nerve Stimulation. In: Kitchen, S. ed. *Electrotherapy: Evidence Based Practice*. 11<sup>th</sup> Ed. Edinburgh, Churchill Livingstone.

Johnson, M.I. 2007. Transcutaneous electrical nerve stimulation: mechanisms, clinical application and evidence. *British Journal of Pain*. 1(1); pp 7–11

Johnson, M.I., Ashton, C.H., Thompson, J.W. 1991 An in-depth study of long-term users of transcutaneous electrical nerve stimulation (TENS). Implications for the use of TENS. *Pain*. 44; pp 221-229

Johnson, M.I. and Bjordal, J.M. 2011. Transcutaneous electrical nerve stimulation for the management of painful conditions: focus on neuropathic pain. *Expert Review of Neurotherapeutics*. 11(5); pp 735–753

Johnson, M.I. and Tabasam, G. 2003. An investigation into the analgesic effects of interferential currents and transcutaneous electrical nerve stimulation on experimentally induced ischemic pain in otherwise pain-free volunteers. *Physical Therapy*. 83(3); pp 208-223

Johnson, M.I. and Martinson, M. 2007 Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: a meta-analysis of randomized controlled trials. *Pain*. 130; pp 157-165

Johnson, M.A., Polgar, J., Weightman, D., Appleton, D. 1973. Data on the distribution of fibre types in thirty-six human muscles. An autopsy study. *Journal of the Neurological Sciences*. 18(1); pp 111–129

Jorenby, D.E., Leischow, S.J., Nides, M.A., Rennard, S.I., Johnston, J.A., Hughes, A.R. 1999. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *New England Journal of Medicine*. 340(9); pp 685-691

Kakkos, S.K., Geroulakos, G., Nicolaides, A.N. 2005. Improvement of the walking ability in intermittent claudication due to superficial femoral artery occlusion with supervised exercise and pneumatic foot and calf compression: a randomised controlled trial. *European Journal of Vascular and Endovascular Surgery*. 30; pp 164-175

Kalra, A., Urban, M.O., Sluka, K.A. 2001. Blockade of opioid receptors in rostral ventral medulla prevents antihyperalgesia produced by transcutaneous electrical nerve stimulation (TENS). *The Journal of Pharmacology and Experimental Therapeutics*. 298(1); pp 257–263

Kam, P.C.A. 2007. Uses and precautions of tourniquets. *The Foundation Years*. 3(5); pp 228-229

Karoly, P. and Ruehlman, L.S. 2007. Psychosocial aspects of pain-related life task interference: an exploratory analysis in a general population sample. *Pain Medicine*. 8(7); pp 563–572

Katz J. 1992. Psychophysical correlates of phantom limb experience. *Journal of Neurology, Neurosurgery and Psychiatry*. 55; pp 811-821

Katz J. and Melzack R. 1991. Auricular Transcutaneous Electrical Nerve Stimulation (TENS) reduces phantom limb pain. *Journal of Pain and Symptom Management*. 6; pp 73-83

Katz, J. and Melzack, R. 1999. Measurement of pain. *Surgical Clinics of North America*. 79(2); pp 231–252

Katz, J., Clairoux, M., Kavanagh, B.P., Roger, S., Nierenberg, H., Redahan, C., Sandler, A.N. 1994. Pre-emptive lumbar epidural anaesthesia reduces postoperative pain and patient-controlled morphine consumption after lower abdominal surgery. *Pain*. 59(3); pp 395–403

Keefe, F.J., Lefebvre, J.C., Maixner, W., Salley, A.N.Jr., Caldwell, D.S. 1997. Self-efficacy for arthritis pain: Relationship to perception of thermal laboratory pain stimuli. *Arthritis & Rheumatism*. 10(3); pp 177–184

Keefe, F.J. Rumble, M.E., Scipio, C.D., Giordano, L.A., Perri, L.M. 2004. Psychological aspects of persistent pain: current state of the science. *Journal of Pain*. 5(4); pp 195-211

Kendell, K., Saxby, B., Farrow, M., Naisby, C. 2001. Psychological factors associated with short-term recovery from total knee replacement. *British Journal of Health Psychology*. 6(1); pp 41–52

Kennedy, A., Reeves, D., Bower, P., Lee, V., Middleton, E., Richardson, G., Gardner, C., Gately, C., Rogers, A. 2007. The effectiveness and cost effectiveness of a national lay-led self care support programme for patients with long-term conditions: a pragmatic randomised controlled trial. *Journal of Epidemiology & Community Health*. 61(3); pp 254–261

Khadilkar, A., Odebiyi, D.O., Brosseau, L., Wells, G.A. 2008. Transcutaneous electrical nerve stimulation (TENS) versus placebo for chronic low-back pain. *Cochrane Database Systematic Reviews* Issue 4 CD003008

Khan, S., Flather, M., Mister, R., Delahunty, N., Fowkes, G., Bradbury, A., Stansby, G. 2007. Characteristics and Treatments of Patients with Peripheral Arterial Disease Referred to UK Vascular Clinics: Results of a Prospective Registry. *European Journal of Vascular & Endovascular Surgery*. 33(4); pp 442–450

Kieffer, E., Bahnini, A., Mouren, X., Gamand, S. 2001. A new study demonstrates the efficacy of naftidrofuryl in the treatment of intermittent claudication. Findings of the Naftidrofuryl Clinical Ischemia Study (NCIS). *International Angiology*. 20(1); pp 58-65

Kiernan, M.C.M., Hales, J.P.J., Gracies, J.M.J., Mogyoros, I.I., Burke, D.D. 1997. Paraesthesiae induced by prolonged high frequency stimulation of human cutaneous afferents. *The Journal of Physiology*. 501(2); pp 461–471

King, S., Vanicek, N., Mockford, K.A., Coughlin, P.A. 2012. The effect of a 3-month supervised exercise programme on gait parameters of patients with peripheral arterial disease and intermittent claudication. *Clinical Biomechanics*. 27(8); pp 845–851

Kitzinger, J. 1994. The methodology of focus groups: the importance of interaction between research participants. *Sociology of Health and Illness*. 16(1); pp 103-121

Klepac R.K., Dowling J., Hauge G. 1981 Sensitivity of the McGill Pain Questionnaire to intensity and quality of laboratory pain. *Pain*. 10; pp 199-207

Klevsgard, R., Hallberg, I.R., Risberg, B., Thomsen, M.B., 1999. Quality of life associated with varying degrees of chronic lower limb ischaemia; comparison with a healthy sample. *European Journal of Vascular and Endovascular Surgery*. 17; pp 319–325

Kruidenier, L.M., Nicolai, S.P.A., Bosch, Ten, J.A., de Bie, R.A., Prins, M.H., Teijink, J.A.W. 2009a. Predictors of walking distance after supervised exercise therapy in patients with intermittent claudication. *European Journal of Vascular & Endovascular Surgery*. 38(4); pp 449–455

Kruidenier, L.M., Nicolai, S.P., Willigendael, E.M., de Bie, R.A., Prins, M.H., Teijink, J.A. 2009b. Functional claudication distance: a reliable and valid measurement to assess functional limitation in patients with intermittent claudication. *BMC Cardiovascular Disorders*. 9(9); pp 1–7

Kruidenier, L.M., Nicolai, S.P., Hendriks, E.J., Bollen, E.C., Prins, M.H., Teijink, J.A.W. 2009c. Supervised exercise therapy for intermittent claudication in daily practice. *Journal of Vascular Surgery* 49(2); pp 363–370

Kunz, R. and Oxman, A.D. 1998. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *British Medical Journal*. 317; pp 1185-1190

Labs, K.H., Nehler, M.R., Roessner, M., Jaeger, K.A., Hiatt, W.R. 1999. Reliability of treadmill testing in peripheral arterial disease: a comparison of a constant load with a graded load treadmill protocol. *Vascular Medicine*. 4(4); pp 239–246

Lang, P.M., Schober, G.M., Rolke, R., Wagner, S., Hilge, R., Offenbacher, M., Treede, R-D., Hoffmann, U., Irnich, D. 2006, Sensory neuropathy and signs of central sensitization in patients with peripheral arterial disease. *Pain*. 124(1); pp 190-200

Lang, P.M., Rüger, L.J., Abahji, T., Hoffmann, U., Crispin, A., Irnich, D. 2009. Correlation between quantitative sensory testing and questionnaires on neuropathic pain for chronic ischemic pain in peripheral arterial disease. *Der Schmerz*. 23(3); pp 251-256

Langley, G.B., Sheppeard, H., Johnson, M., Wigley, R.D. 1984. The analgesic effects of transcutaneous electrical nerve stimulation and placebo in chronic pain patients. *Rheumatology International*. 4; pp 119–123

Large, R.G. 1996. Psychological aspects of pain. *Annals of the Rheumatic Diseases*. 55(6); pp 340–345

Laurenzano, E., Spadera, L., De Laurentis, M., Brevetti, G. 2009. Impairment of microcirculation and energy metabolism in intermittent claudication: beneficial effects of exercise training. *Monaldi Archives of Chest Diseases*. 72; pp 110–117

Lauret, G.-J., Gijsbers, H.J.H., Hendriks, E.J., Bartelink, M.-L., de Bie, R.A., Teijink, J.A.W. 2012. The ClaudicationNet concept: design of a national integrated care network providing active and healthy aging for patients with intermittent claudication. *Vascular Health and Risk Management*. 8; pp 495–503

Law, P.P.W. and Cheing, G.L.Y. 2004. Optimal stimulation frequency of transcutaneous electrical nerve stimulation on people with knee osteoarthritis. *Journal of Rehabilitation Medicine*. 36; pp 220–225

Lawn, S., McMillan, J., Pulvirenti, M. 2011. Chronic condition self-management: Expectations of responsibility. *Patient Education and Counseling*. 84(2); pp e5–e8

Layden, J., Michaels, J., Bermingham, S., Higgins, B. 2012. Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance. *British Medical Journal*. 345; pp e4947

Le Bars, D. 2002. The whole body receptive field of dorsal horn multireceptive neurones. *Brain Research Reviews*. 40; pp 29–44

Le Faucheur, A., Abraham, P., Jaquinandi, V., Bouye, P., Saumet, J.L., Noury-Desvaux, B. 2008. Measurement of walking distance and speed in patients with peripheral arterial disease: a novel method using a global positioning system. *Circulation*. 117(7); pp 897–904

Lee, H.L.D., Mehta, T., Ray, B., Heng, M.S.T., McCollum, P.T., Chetter, I.C. 2007. A non-randomised controlled trial of the clinical and cost effectiveness of a supervised exercise programme for claudication. *European Journal of Vascular & Endovascular Surgery*. 33(2); pp 202–207

Lee, K.H., Chung, J.M., Willis, W.D. 1985. Inhibition of primate spinothalamic tract cells by TENS. *Journal of Neurosurgery*. 62(2); pp 276–287

Leeuw, M., Goossens, M.E., Linton, S.J., Crombez, G., Boersma, K., Vlaeyen, J.W.S. 2007. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *Journal of Behavioural Medicine*. 30; pp 77–94

Lehert, P., Comte, S., Gamand, S., Brown, T.M. 1994. Naftidrofuryl in intermittent claudication: a retrospective analysis. *Journal of Cardiovascular Pharmacology*. 23(Suppl 3); pp S48-S52

Leng, G.C. Fowler, B. Ernst, E. 2000. Exercise for intermittent claudication. *The Cochrane Database of Systematic Reviews*. Issue 2.

Lewis T. 1932. Pain in muscular ischemia. *Archives of Internal Medicine*. 49; pp 713

Lincoln, Y.S. and Guba, E.G. 1985. *Naturalistic Inquiry*. Sage Publications, London, UK.

Linde, K., Witt, C.M., Streng, A., Weidenhammer, W., Wagenpfeil, S., Brinkhaus, B., Willich, S.N., Melchart, D. 2007. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. *Pain*. 128(3); pp 264–271

Loeser, J.D. and Melzack, R. 1999. Pain: an overview. *The Lancet*. 353(9164); pp 1607–1609

Lonn, E., Yusuf, S., Arnold, M.J., Sheridan, P., Pogue, J., Micks, M. 2006. Homocysteine lowering with folic acid and B vitamins in vascular disease. *New England Journal of Medicine*. 354(15); pp 1567-1577

Lorig, K., Chastain, R.L., Ung, E., Shoor, S., Holman, H.R. 1989. Development and evaluation of a scale to measure perceived self-efficacy in people with arthritis. *Arthritis and Rheumatism*. 32; pp 37-44

Lorig, K.R., Sobel, D.S., Ritter, P.L., Laurent, D., Hobbs, M. 2001. Effect of a self-management program on patients with chronic disease. *Effective Clinical Practice*. 4; pp 256-262

Lorig, K.R., Ritter, P.L., Dost, A., Plant, K., Laurent, D.D. Mcneil, I. 2008. The expert patients programme online, a 1-year study of an Internet-based self-management programme for people with long-term conditions. *Chronic Illness*. 4(4); pp 247–256

Love, A., Leboeuf, C., Crisp, T.C. 1989. Chiropractic chronic low back pain sufferers and self-report assessment methods. Part i. A reliability study of the visual analogue scale, the pain drawing and the McGill Pain Questionnaire. *Journal of Manipulative Physiological Therapies*. 12; pp 21–25

Lowe, N.K., Walker, S.N., MacCallum, R.C. 1991. Confirming the theoretical structure of the McGill Pain Questionnaire in acute clinical pain. *Pain*. 46; pp 53-60

Luijpen, M.W., Swaab, D.F., Sergeant, J.A., Scherder, E.J.A. 2004. Effects of transcutaneous electrical nerve stimulation (TENS) on self-efficacy and mood in elderly with mild cognitive impairment. *Neurorehabilitation and Neural Repair*. 18(3); pp 166–175



Ma, Y.T. and Sluka, K.A. 2001. Reduction in inflammation-induced sensitization of dorsal horn neurons by transcutaneous electrical nerve stimulation in anesthetized rats. *Experimental Brain Research*. 137(1); pp 94–102

Macdonald, W., Rogers, A., Blakeman, T., Bower, P. 2008. Practice nurses and the facilitation of self-management in primary care. *Journal of Advanced Nursing*. 62(2); pp 191–199

Mackay, C., Scott, K., McMillan, D. 2007, A comparison study into the effects of experimentally induced ischemia in standing and supine on pain perception and psychological wellbeing. BSc (Hons) Physiotherapy edn, Queen Margaret University, Queen Margaret University, Edinburgh, UK. Unpublished observations

Maeda, Y., Lisi, T.L., Vance, C.G.T., Sluka, K.A. 2007. Release of GABA and activation of GABAA in the spinal cord mediates the effects of TENS in rats. *Brain Research*. 1136; pp 43–50

Main, C.J. and Watson, P.J. 1999. Psychological aspects of pain. *Manual Therapy*. 4(4); pp 203–215

Makris, G.C., Lattimer, C.R., Lavidia, A., Geroulakos, G. 2012. Availability of Supervised Exercise Programs and the Role of Structured Home-based Exercise in Peripheral Arterial Disease. *European Journal of Vascular & Endovascular Surgery*. 44(6); pp 569–575.

Manheimer, C., Lund, S., Carlsson, C.A. 1978. The effect of transcutaneous electrical nerve stimulation (TENS) on joint pain in patients with RA. *Scandinavian Journal of Rheumatology*. 7; pp 13–16

Marchand, S., Charest, J., Li, J., Chenard, JR., Lavignolle, B., Laurencelle, L. 1993. Is TENS purely a placebo effect? A controlled study on chronic low back pain. *Pain*. 54; pp 99-106

Martin, M.Y., Bradley, L.A., Alexander, R.W., Alarcón, G.S., Triana-Alexander, M., Aaron, L.A., Alberts, K.R. 1996. Coping strategies predict disability in patients with primary fibromyalgia. *Pain*. 68(1); pp 45–53

Matsuo, H. and Shigematsu, H. 2010. Patient-based outcomes using the walking impairment questionnaire for patients with peripheral arterial occlusive disease treated with Lipo-PGE<sub>1</sub>. *Circulation Journal*. 74; pp 365-370

Mayer, E.A., Berman, S., Suyenobu, B., Labus, J., Mandelkern, M.A., Naliboff, B.D., Chang, L. 2005. Differences in brain responses to visceral pain between patients with irritable bowel syndrome and ulcerative colitis. *Pain*. 115(3); pp 398–409

Mazari, F.A.K., Khan, J.A., Carradice, D., Samuel, N., Abdul Rahman, M.N.A., Gulati, S., Lee, H.L.D., Mehta, T.A., McCollum, P.T., Chetter, I.C. 2011. Randomized clinical trial of percutaneous transluminal angioplasty, supervised exercise and combined treatment for

intermittent claudication due to femoropopliteal arterial disease. *British Journal of Surgery*. 99(1); pp 39–48

McCracken, L.M., Zayfert, C., Gross, R.T. 1992. The Pain Anxiety Symptoms Scale: development and validation of a scale to measure fear of pain. *Pain*. 50(1); pp 67–73

McCracken, L.M. 1997. 'Attention' to pain in persons with chronic pain: A behavioral approach. *Behavior Therapy*. 28(2); pp 271–284

McCracken, L.M. and Gross, R.T. 1993. Does anxiety affect coping with chronic pain? *Clinical Journal of Pain*. 9; pp 253–259

McDermott, M.M., Mehta, S., Liu, K., Guralnik, J.M., Martin, G.J., Criqui, M.H., Greenland, P. 1999. Leg symptoms, the ankle-brachial index, and walking ability in patients with peripheral arterial disease. *Journal of General Internal Medicine*. 14(3); pp 173–181

McDermott, M.M., Greenland, P., Guralnik, J.M., Liu, K., Criqui, M.H., Pearce, W.H., Chan, C., Schneider, J., Sharma, L., Taylor, L.M. Arseven, A., Quann, M., Celic, L. 2003. Depressive symptoms and lower extremity functioning in men and women with peripheral arterial disease. *Journal of General and Internal Medicine*. 18; pp 461–467

McDermott, M.M.G., Liu, K., Ferrucci, L., Criqui, M.H., Greenland, P., Guralnik, J.M., Tian, L., Schneider, J.R., Pearce, W.H., Tan, J. 2006. Physical performance in peripheral arterial disease: a slower rate of decline in patients who walk more. *Annals of Internal Medicine*. 144(1); pp 10–20

McDermott, M.M., Ades, P., Guralnik, J.M., Dyer, A., Ferrucci, L., Liu, K., Nelson, M., Lloyd-Jones, D., van Horn, L., Garside, D., Kibbe, M., Domanchuk, K., Stein, J.H., Liao, Y., Tao, H., Green, D., Pearce, W.H. Schneider, J.R., McPherson, D., Laing, S.T., McCarthy, W.J., Shroff, A., Criqui, M.H. 2009. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication. *Journal of the American Medical Association*. 301(2); pp 165–174

McDermott, M.M.G., Liu, K., Guralnik, J.M., Martin, G.J., Criqui, M.H., Greenland, P. 1998. Measurement of walking endurance and walking velocity with questionnaire: validation of the walking impairment questionnaire in men and women with peripheral arterial disease. *Journal of Vascular Surgery*. 28(6); pp 1072–1081

McDermott, M.M., Mazor, K.M., Reed, G., Pagoto, S., Graff, R., Merriam, P., Kibbe, M., Greenland, P., Ockene, J., Olendzki, B., Tao, H., Ockene I. 2010. Attitudes and behavior of peripheral arterial disease patients toward influencing their physician's prescription of cholesterol-lowering medication. *Vascular Medicine*. 15(2); pp 83–90

McDermott, M.M., Reed, G., Greenland, P., Mazor, K.M., Pagoto, S., Ockene, J.K., Graff, R., Merriam, P.A., Leung, K., Manheim, L., Kibbe, M.R., Olendzki, B., Pearce, W.H., Ockene, I.S.

2011. Activating peripheral arterial disease patients to reduce cholesterol: a randomized trial. *The American Journal of Medicine*. 124(6); pp 557–565

McNeil, D.W. and Rainwater, A.J. 1998. Development of The Fear Of Pain Questionnaire – III. *Journal of Behavioural Medicine*. 21(4); pp 389-410

Meleis, A.I., Sawyer, L.M., Im, E.O., Hilfinger Messias, D.K., Schumacher, K. 2000. Experiencing transitions: an emerging middle-range theory. *Advances in Nursing Science*. 23(1); pp 12–28

Melzack, R. 1975. The McGill Pain Questionnaire: Major properties and scoring methods. *Pain*. 1; pp 277-299

Melzack, R. (Ed) 1983. *Pain measurement and assessment*. New York: Raven Press.

Melzack, R. 1984. The myth of painless childbirth. *Pain*. 19; pp 331-337

Melzack, R. 1987. The short-form McGill Pain Questionnaire. *Pain*. 30; pp 191-197

Melzack, R. 1999. From the gate to the neuromatrix. *Pain*. Suppl. 6; pp S121-S126

Melzack, R. 2001. Pain and the neuromatrix in the brain. *Journal of Dental Education*. 65; pp 1378–1382

Melzack, R. and Casey, K.L. 1968. Sensory, motivational, and central control determinants of pain. A new conceptual model. In D. R. Kenshalo Eds. *The Skin Senses*. Springfield, Illinois, Charles C. Thomas. pp 423-443

Melzack, R., Coderre, T.J., Katz, J., Vaccarino, A.L. 1981. Labour is still painful after prepared childbirth training. *Canadian Medical Association Journal*. 125(4); pp 357-363

Melzack, R. and Katz, J. 2012. Pain. *Wiley Interdisciplinary Reviews: Cognitive Science*. 4(1); pp 1–15

Melzack, R., Katz, J., Jeans, M.E. 1985. The role of compensation in chronic pain: analysis using a new method of scoring the McGill Pain Questionnaire. *Pain*. 23(2); pp 101-112

Melzack, R., and Loeser, J.D. 1978. Phantom body pain in paraplegics: evidence for a central 'pattern generating mechanism' for pain. *Pain*. 4; pp 195-210

Melzack, R. and Torgerson, W.S. 1971. On the language of pain. *Anesthesiology*. 34; pp 50-59

Melzack, R. and Wall, P.D. 1965. Pain mechanisms: a new theory. *Science*. 150(699); pp 971–979

Melzack, R. and Wall, P.D. 1996. *The Challenge of Pain*. Updated 2<sup>nd</sup> Ed. Middlesex: Penguin Books.

Merskey, H. and Bogduk, N. 1994. *Classification of chronic pain. Definitions of Chronic Pain Syndromes and Definition of Pain Terms*. 2nd ed. International Association for the Study of Pain: Seattle.

Meru, A.V., Mittra, S., Thyagarajan, B., Chugh, A. 2006. Review: intermittent claudication: an overview. *Atherosclerosis*. 187; pp 221-237

Milani, R.V. and Lavie, C.J. 2007. The role of exercise training in peripheral arterial disease. *Vascular Medicine*. 12(4); pp 351-358

Miller, J.F. 2000. *Coping with Chronic Illness*. 3<sup>rd</sup> Ed. Philadelphia: F.A. Davis

Miller, R.P., Kori, S.H., Todd, D.D., 1991. The Tampa Scale. Unpublished Report, Tampa, FL.

Mogyoros, I., Bostock, H., Burke, D. 2000. Mechanisms of paresthesias arising from healthy axons. *Muscle & Nerve*. 23(3); pp 310–320

Mohler III, E.R., Hiatt, W.R., Creager, M.A. 2003. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation*. 108; pp 1481-1486

Moher, D., Pham, B., Aulsebrook, M., Saenz, A., Hood, S., Barber, G. 2000. Pharmacological management of intermittent claudication: a meta- analysis of randomised trials. *Drugs*. 59(5); pp 1057-1070

Momsen, A.H., Jensen, M.B., Norager, C.B., Madsen, M.R., Vestersgaard-Andersen, T., Lindholt, J.S. 2009. Drug therapy for improving walking distance in intermittent claudication: a systematic review and meta-analysis of robust randomised controlled studies. *European Journal of Vascular and Endovascular Surgery*. 38(4); pp 463-474

Mondillo, S., Ballo, P., Barbati, R., Guerrini, F., Ammaturo, T., Agricola, E., Pastore, M., Borrello, F., Belcastro, M., Picchi, A., Nami, R. 2003. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. *The American Journal of Medicine*. 114(5); pp 359 - 364.

Montgomery, G.H. and Kirsch, I. 1997. Classical conditioning and the placebo effect. *Pain*. 72; pp 107–113

Moore, P.A., Duncan, G.H., Scott, D.S., Gregg, J.M., Ghia, J.N. 1979. The submaximal effort tourniquet test: its use in evaluating experimental and chronic pain. *Pain*. 6(3); pp 375–382

- Moore, D.J., Keogh, E., Eccleston, C. 2012. The interruptive effect of pain on attention. *The Quarterly Journal of Experimental Psychology*. 65(3); pp 565–586
- Moore, D.J., Keogh, E., Eccleston, C. 2013. The effect of threat on attentional interruption by pain. *Pain*. 154(1); pp 82–88
- Morgan, M.B.F., Crayford, T., Murrin, B., Fraser, S.C. 2001. Developing the Vascular Quality of Life Questionnaire: A new disease-specific quality of life measure for use in lower limb ischemia. *Journal of Vascular Surgery*. 33; pp 679-687
- Murabito, J. M., Evans, J. C., Nieto, K., Larson, M. G., Levy, D., Wilson, P. W. F. 2002. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. *American Heart Journal*. 143(6); pp 961-965
- National Institute for Health and Clinical Excellence (NICE) 2009. *Draft scope for the proposed appraisal of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease*. National Institute for Health and Clinical Excellence, UK.
- Neergaard, M., Olesen, F., Andersen, R., Sondergaard, J. 2009. Qualitative description – the poor cousin of health research? *BMC Medical Research Methodology*. 9(1); pp 1-5
- Ngamkham, S., Vincent, C., Finnegan, L., Holden, J.E., Wang, Z.J., Wilkie, D.J. 2012. The McGill Pain Questionnaire as a multidimensional measure in people with cancer: an integrative review. *Pain Management Nursing*. 13(1); pp 27–51
- Nicholas, M.K. 2007, The pain self-efficacy questionnaire: taking pain into account, *European Journal of Pain*. 11(2); pp 153-163
- Nicholas, M.K., Asghari, A., Blyth, F.M. 2008. What do the numbers mean? Normative data in chronic pain measures. *Pain*. 134; pp 158-173
- Nicolaï, S.P.A., Kruidenier, L.M., Rouwet, E.V., Graffius, K., Prins, M.H., Teijink, J.A.W. 2009a. The walking impairment questionnaire: An effective tool to assess the effect of treatment in patients with intermittent claudication. *Journal of Vascular Surgery*. 50(1); pp 89-94
- Nicolaï, S.P.A., Viechtbauer, W., Kruidenier, L.M., Candel, M.J.J.M., Prins, M.H., Teijink, J.A.W. 2009b. Reliability of treadmill testing in peripheral arterial disease: A meta-regression analysis. *Journal of Vascular Surgery*. 50(2); pp 322–329
- Nicolaï, S.P.A., Leffers, P., Kruidenier, L.M., De Bie, R.A., Prins, M.H., Teijink, J.A.W. 2010. Extending the range of treadmill testing for patients with intermittent claudication. *Medicine and Science in Sport and Exercise*. 42(4); pp 640-645

Niv, D. and Devor, M. 2004. Chronic pain as a disease in its own right. *Pain Practice*. 4(3); pp 179-181

Nnoaham, K. and Kumbang, J. 2008. Transcutaneous electrical nerve stimulation (TENS) for chronic pain. *Cochrane Database of Systematic Reviews* 3.

Norgren, L., Hiatt, W.R., Dormandy, J.A., Nehler, M.R., Harris, K.A., Fowkes, F.G.R. 2007. Inter-society consensus for the management of peripheral arterial disease (TASC II). *Journal of Vascular Surgery*. 45(1); pp S5–S67.

Norlyk, A. and Harder, I. 2010. What Makes a Phenomenological Study Phenomenological? An Analysis of Peer-Reviewed Empirical Nursing Studies. *Qualitative Health Research*. 20(3); pp 420–431

Oakley, C., Zwierska, I., Tew, G., Beard, J.D., Saxton, J.M. 2008. Nordic poles immediately improve walking distance in patients with intermittent claudication. *European Journal of Vascular and Endovascular Surgery*. 36; pp 689-694

O'Donnell, M.E., Badger, S.A., Sharif, M.A., Young, I.S., Lee, B., Soong, C.V. 2009. The vascular and biochemical effects of cilostazol in patients with peripheral arterial disease. *Journal of Vascular Surgery*. 49; pp 1226-1234

Oka, R.K., Szuba, A., Giacomini, J.C., Cooke, J.P. 2003. Gender differences in perception of PAD: a pilot study. *Vascular Medicine*. 8(2); pp 89–94

Olin, J.W., Allie, D.E. Belkin, M., Bonow, R.O., Casey, D.E.Jr., Creager, M.A., Gerber, T.C., Hirsch, A.T., Jaff, M.R., Kaufman, J.A., Lewis, C.A., Martin, E.T., Martin, L.G., Sheelan, P., Stewart, K.J., Treat-Jacobson, D., White, C.J., Zheng, Z-J. 2010. ACCF/AHA/ACR/SCAI/SIR/SVM/SVN/SVS 2010 performance measures for adults with peripheral artery disease. A report of the American College Of Cardiology Foundation/American Heart Association task force on performance measures, the American College Of Radiology, the Society For Cardiac Angiography And Interventions, the Society For Interventional Radiology, the Society For Vascular Medicine, the Society For Vascular Nursing, and the Society For Vascular Surgery (writing committee to develop clinical performance measures for peripheral artery disease). *Circulation*. 122; pp 2583-2618

Osiri, M., Welch, V., Brosseau, L., Shea, B., McGowan, J.L., Tugwell, P., Wells, G.A. 2000. Transcutaneous electrical nerve stimulation for knee osteoarthritis. *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD002823

Ottenbacher, K.J. and Maas, S. 1999. How to detect effects: statistical power and evidence based practice in occupational therapy research. *American Journal of Occupational Therapy*. 53; pp 181-188

Oxford Dictionaries. 2010. Oxford University Press.  
<http://oxforddictionaries.com/definition/english/psychosocial> (accessed November 03, 2012).

Pantaleão, M.A., Laurino, M.F., Gallego, N.L.G., Cabral, C.M.N., Rakel, B., Vance, C., Sluka, K.A., Walsh, D.M., Liebano, R.E. 2011. Adjusting pulse amplitude during transcutaneous electrical nerve stimulation (tens) application produces greater hypoalgesia. *The Journal of Pain*. 12(5); pp 581–590

Papageorgiou, A.C. and Badley, E.M. 1989. The quality of pain in arthritis: the words patients use to describe overall pain and pain in individual joints at rest and on movement. *Journal of Rheumatology*. 16; pp 106–112

Parker, J.C., Callahan, C.D., Smarr, K.L., McClure, K.W., Stucky-Ropp, R.C., Anderson, S.K., Walker, S.E. 1993. Relationship of pain behavior to disease activity and health status in rheumatoid arthritis. *Arthritis Care and Research*. 6; pp 71-77

Parr, B.B., Noakes, T.D.T., Derman, E.W.E. 2008. Factors predicting walking intolerance in patients with peripheral arterial disease and intermittent claudication. *South African Medical Journal/Suid-Afrikaanse Mediese Tydskrift*. 98(12); pp 958–962

Parr, J.J., Borsa, P.A., Fillingim, R.B., Tillman, M.D., Manini, T.M., Gregory, C.M., George, S.Z. 2012. Pain-related fear and catastrophizing predict pain intensity and disability independently using an induced muscle injury model. *The Journal of Pain*. 13(4); pp 370–378

Pell, J.P. 1995. Impact of Intermittent claudication on quality of life. *European Journal of Vascular and Endovascular Surgery*. 9; pp 469-472

Pertovaara, A., Nurmikko, T., Pöntinen, P.I. 1984. Two separate components produced by the submaximal effort tourniquet test. *Pain*. 20; pp 53-58

Posner, J. 1984. A modified submaximal effort tourniquet test for evaluation of analgesics in healthy volunteers. *Pain*. 19(2); pp 143–151

Pratt, C. 2001. Analysis of the cilostazol safety database. *American Journal of Cardiology*. 87(12A); pp 28D-33D

Price, D.D., Milling, L.S. Kirsch, I., Duff, A., Montgomery, G.H., Nicholls, S.S. 1999. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain*. 83; pp 147-156

Price, D.D., Finniss, D.G., Benedetti, F. 2008. A comprehensive review of the placebo effect: recent advances and current thought. *Annual Review of Psychology*. 59(1); pp 565–590

Quartana, P.J., Campbell, C.M., Edwards, R.R. 2009. Pain catastrophizing: a critical review. *Expert Review of Neurotherapeutics*. 9(5); pp 745–758

Radhakrishnan, R., King, E.W., Dickman, J.K., Herold, C.A., Johnston, N.F., Spurgin, M.L., Sluka, K.A. 2003. Spinal 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors mediate low, but not high, frequency TENS-induced antihyperalgesia in rats. *Pain*. 105(1-2); pp 205–213

Radhakrishnan, R. and Sluka, K.A. 2005. Deep tissue afferents, but not cutaneous afferents, mediate transcutaneous electrical nerve stimulation induced antihyperalgesia. *Journal of Pain*. 6(10); pp 673–80

Rainville, P., Bao, Q.V.H., Chrétien, P. 2005. Pain-related emotions modulate experimental pain perception and autonomic responses. *Pain*. 118(3); pp 306–318

Regensteiner, J.G., Steiner, J.F., Hiatt, W.R. 1996. Exercise training improves functional status in patients with peripheral arterial disease. *Journal of Vascular Surgery*. 23; pp 104-15

Regensteiner, J.G., Steiner, J.F., Panzer, R.J., Hiatt, W.R. 1990. Evaluation of walking impairment by questionnaire in patients with peripheral arterial disease. *Journal of Vascular Medicine and Biology*. 2; pp 142-152 (Appendix I pages 150-151)

Regensteiner, J.G.P. and Treat-Jacobson, D.R.P. 2001. Review: exercise programmes increase walking times in patients with intermittent claudication. *Evidence-Based Nursing*. 4(1); pp 21

Regensteiner, J., Ware, J.J., McCarthy, W., Zhang, P., Forbes, W., Heckman, J., Hiatt, W.R. 2002. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. *Journal of the American Geriatric Society*. 50(12); pp 1939-1946

Rieger, H. and Scheffler, A. 1999, Pain in chronic peripheral arterial occlusive disease. Pathogenesis and therapy, *Internist (Berlin)*. 40(2); pp 133-139

Roche, P.A., Belch, J.J.F., Ellis, B., Raza, Z., McCaldin, D. 2005. Pain in Intermittent Claudication: Relations between walking and cognitive-behavioural factors in peripheral arterial disease- a pilot study. *International Association for the Study of Pain*. 11<sup>th</sup> World Congress on Pain. Sydney, Australia. 2005

Roche, P.A. and Gijsbers, K. 1986. A comparison of memory for induced ischaemic pain and chronic rheumatoid pain. *Pain*. 25; pp 337-343

Roche, P.A., Gijsbers, K., Belch, J.J.F., Forbes, C.D. 1984. Modification of induced ischaemic pain by transcutaneous electrical nerve stimulation. *Pain*. 20; pp 45-52



Roche, P.A. and Heim, H.M. 1997. Pain in prostate cancer patients with and without metastases. *The Pain Clinic*. 10(1); pp 9-17

Roche, P.A., Klestov, A.C., Heim, H.M. 2003. Description of stable pain in rheumatoid arthritis: a 6 year study. *Journal of Rheumatology*. 30; pp 1733-1738

Roche, P.A., Santos, D., Seenan, C., Snijder, J., Weddell, A., Sweers, I., Ham, E., 2007. A model of ischemic pain in the calf and TENS modification of lower limb pain: preliminary results in: World Physical Therapy 2007 — Abstracts. *Physiotherapy*. 2007; 93; pp S52

Roche, P.A., Tan, H., Stanton, W.R. 2002. Modification of induced ischaemic pain by placebo electrotherapy. *Physiotherapy Theory and Practice*. 18; pp 131-139

Roelofs, J., van Breukelen, G., Sluiter, J., Frings-Dresen, M.H.W., Goosens, M., Thibault, P., Boersma, K., Vlaeyen, J.W.S. 2011. Norming of the Tampa Scale of Kinesiophobia across pain diagnoses and various countries. *Pain*. 152; pp 1090-1095

Roger, V.L., Go, A.S., Lloyd-Jones, D.M., Adams, R.J., Berry, J.D., Brown, T.M., Carnethon, M.R., Dai, S., de Simone, G., Ford, E.S., Fox, C.S., Fullerton, H.J., Gillespie, C., Greenlund, K.J., Hailpern, S.M., Heit, J.A., Ho, P.M., Howard, V.J., Kissela, B.M., Kittner, S.J., Lackland, D.T., Lichtman, J.H., Lisabeth, L.D., Makuc, D.M., Marcus, G.M., Marelli, A., Matchar, D.B., McDermott, M.M., Meigs, J.B., Moy, C.S., Mozaffarian, D., Mussolino, M.E., Nichol, G., Paynter, N.P., Rosamond, W.D., Sorlie, P.D., Stafford, R.S., Turan, T.N., Turner, M.B., Wong, N.D., Wylie-Rosett, J. 2011. Heart Disease and Stroke Statistics– 2011 Update: A Report From the American Heart Association. *Circulation*. 123; pp e18-e209

Romano, J.M. and Turner, J.A. 1985. Chronic pain and depression: does the evidence support a relationship? *Psychological Bulletin*. 97(1); pp 18–34

Rosenstiel, A.K. and Keefe, F.J. 1983. The use of coping strategies in chronic low back pain patients: relationship to patient characteristics and current adjustment. *Pain*. 17(1); pp 33–44

Rosenblatt, R.M. and Hetherington, A. 1981. Failure of Transcutaneous Electrical Nerve Stimulation to Alleviate Experimental Tourniquet Pain. *Anesthesia and Analgesia*. 60(10); pp 720-722.

Rüger, L.J., Irnich, D., Abahji, T.N., Crispin, A., Hoffmann, U., Lang, P.M. 2008. Characteristics of chronic ischemic pain in patients with peripheral arterial disease. *Pain*. 139(1); pp 201-208.

Rutjes, A.W., Nüesch, E., Sterchi, R., Kalichman, L., Hendriks, E., Osiri, M., Brosseau, L., Reichenbach, S., Jüni, P. 2009. Transcutaneous electrostimulation for osteoarthritis of the knee. *Cochrane Database of Systematic Reviews* Issue 4; pp CD002823

Ryan, G.W., Bernard, H.R. 2003. Techniques to Identify Themes. *Field Methods*. 15(1); pp 85–109

Saltin, B., Sjogaard, G., Gaffney, F.A., Rowell, L.B. 1981. Potassium, lactate, and water fluxes in human quadriceps muscle during static contractions. *Circulation Research*. 48(6 II); pp 18-24

Sandelowski, M. 2000. Focus on Research Methods-Whatever Happened to Qualitative Description? *Research in Nursing & Health*. 23; pp 334-340

Sandelowski, M. 2010. What's in a name? Qualitative description revisited. *Research in Nursing & Health*. 33; pp 77-84

Sato, J., Ishii, Y., Noguchi, H., Takeda, M. 2012. Safety and efficacy of a new tourniquet system. *BMC Surgery*. 12(17); pp 1–6

Savage, J. 2000. Ethnography and health care. *BMJ*. 321(7273); pp. 1400–1402

Schillinger, D., Grumbach, K., Piette, J., Wang, F., Osmond, D., Daher, C., Palacios, J., Diaz Sullivan, G., Bindman, A.R. 2002. Association of health literacy with diabetes outcomes. *Journal of American Medical Association*. 288(4); pp 475–482

Schulz, K.F., Chalmers, I., Hayes, R.J., Altman, D.G. 1995. Empirical evidence of bias dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Journal of American Medical Association*. 273(5); pp 408-412

Scott, W., Stevens, J., Binder-Macleod, S.A. 2001. Human skeletal muscle fiber type classifications. *Physical Therapy*. 81(11); pp 1810–1816

Scottish Intercollegiate Guidelines Network (SIGN) 2006. *Diagnosis and management of peripheral arterial disease: a national clinical guideline*. SIGN 89. [Online] Available from [www.sign.ac.uk](http://www.sign.ac.uk) [Accessed 06/01/2008]

Seenan, C., Roche, P.A., Tan, C-W., Mercer, T. 2012. Modification of experimental, lower limb ischemic pain with transcutaneous electrical nerve stimulation. *Clinical Journal of Pain*. 28(8); pp 693-699

Seenan, C., Santos, D., Snijder, J., Weddell, A., Roche, P.A. 2008. Early development of a lower limb ischaemic pain test in healthy volunteers using the McGill Pain Questionnaire. *Proceeding of the 12<sup>th</sup> World Congress on Pain*. IASP Press, Seattle

Selvin, E. and Erlinger, T.P. 2004. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation*. 110(6); pp 738-743

Serizawa, F., Ito, K., Kawamura, K., Tsuchida, K., Hamada, Y., Zukeran, T., Shimizu, T., Akamatsu, D., Hashimoto, M., Goto, H., Watanabe, T., Sato, A., Shimokawa, H., Satomi, S. 2012. Extracorporeal shock wave therapy improves the walking ability of patients with peripheral artery disease and intermittent claudication. *Circulation Journal*. 76(6); pp 1486–1493

Shalhoub, J., Hamish, M., Davies, A.H. 2009. Supervised exercise for intermittent claudication – an under-utilised tool. *Annals of The Royal College of Surgeons of England*. 91(6); pp 473–476

Shanahan, C., Ward, A.R., Robertson, V.J. 2006. Comparison of the analgesic efficacy of interferential therapy and transcutaneous electrical nerve stimulation. *Physiotherapy*. 92(4); pp 247–253

Shenton, A.K. 2004. Strategies for ensuring trustworthiness in qualitative research projects. *Education for Information*. 22; pp 63-75

Siddall, P.J. and Cousins, M.J. 2004. Persistent pain as a disease entity: implications for clinical management. *Anesthesia & Analgesia*. 99(2); pp 510-520

Sim, J. and Wright, C. 2000. *Research in Healthcare: Concepts, Designs and Methods*. Stanley Thornes, Cheltenham

Simpson, J.F. 2007. An investigation into the hypoalgesic effects of Transcutaneous Electrical Nerve Stimulation (TENS) on experimentally induced ischaemia in the lower limb of the standing subject. Unpublished Observations. MSc Dissertation, Queen Margaret University.

Sinclair, D.C. 1955. Cutaneous sensation and the doctrine of specific energy. *Brain*. 78(4); pp 584-614

Sjolund, B., Terenius, L., Eriksson, M. 1977. Increased cerebrospinal fluid levels of endorphins after electroacupuncture. *Acta Physiologica Scandinavia*. 100; pp 382-384

Skevington, S. M. 1995. *The Psychology of Pain*. John Wiley and Sons Ltd. Chichester, UK.

Sluka, K.A., Lisi, T.L., Westlund, K.N. 2006. Increased release of serotonin in the spinal cord during low, but not high, frequency transcutaneous electric nerve stimulation in rats with joint inflammation. *Archives of Physical Medicine and Rehabilitation*. 87(8); pp 1137–1140

Sluka, K.A., Vance, C.G.T., Lisi, T.L. 2005. High-frequency, but not low-frequency, transcutaneous electrical nerve stimulation reduces aspartate and glutamate release in the spinal cord dorsal horn. *Journal of Neurochemistry*. 95(6); pp 1794–1801

Sluka, K.A. and Walsh, D. 2003. Transcutaneous electrical nerve stimulation: basic science mechanisms and clinical effectiveness. *Journal of Pain*. 4(3); pp 109–121

Sluka, K.A., Bailey, K., Bogush, J., Olson, R. Ricketts, A. 1998. Treatment with either high or low frequency TENS reduces the secondary hyperalgesia observed after injection of kaolin and carrageenan into the knee joint. *Pain*. 77(1); pp 97–102

Sluka, K.A., Deacon, M., Stibal, A., Strissel, S., Terpstra, A. 1999. Spinal blockade of opioid receptors prevents the analgesia produced by TENS in arthritic rats. *The Journal of Pharmacology and Experimental Therapeutics*. 289(2); pp 840–846

Smith, G.M., Egbert, L.D., Markowitz, R.A., Mosteller, F., Beecher, H.K. 1966. An experimental pain method sensitive to morphine in man: the submaximal effort tourniquet technique. *The Journal of Pharmacology and Experimental Therapeutics*. 154(2); pp 324-332

Smith, S.C., Jr., Milani, R V., Arnett, D.K., Crouse, J.R., III, McDermott, M.M., Ridker, P.M., Rosenson, R.S., Taubert, K.A., Wilson, P.W.F. 2004. Atherosclerotic vascular disease conference: writing group II: risk factors. *Circulation*. 109(21); pp 2613-2616

Smolderen, K.G.E., Aquarius, A.E., de Vries, J., Smith, O.R.F., Hamming, J.F., Denollet, J. 2008 Depressive symptoms in peripheral arterial disease: a follow-up study on prevalence, stability and risk factors. *Journal of Affective Disorders*. 110; pp 27-35

Smolderen, K.G., Pelle, A.J., Kupper, N., Mols, F., Denollet, J. 2009. Impact of peripheral arterial disease on health status: a comparison with chronic heart failure. *Journal of Vascular Surgery*. 50; pp 1391-1398

Sokolowski, R. 2000. *Introduction to phenomenology*. Cambridge, UK: Cambridge University Press.

Sol, B.G.M., van der Graaf, Y., van Petersen, R., Visseren, F.L.J. 2011. The effect of self-efficacy on cardiovascular lifestyle. *European Journal of Cardiovascular Nursing*. 10(3); pp 180–186

Somers, D.L. and Somers, M.F. 1999. Treatment of neuropathic pain in a patient with diabetic neuropathy using transcutaneous electrical nerve stimulation applied to the skin of the lumbar region. *Physical Therapy*. 79(8); pp 767-775

Spengel, F., Clement, D., Boccalon, H., Liard, F., Brown, T., Leheret, P. 2002. Findings of the Naftidrofuryl in Quality of Life (NIQOL) European study program. *International Angiology*. 21(1); pp 20-27

Squires, H., Simpson, E., Meng, Y., Harnan, S., Stevens, J., Wong, R., Thomas, S., Michaels, J., Stansby, G. 2011. A systematic review and economic evaluation of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease. *Health Technology Assessment (Winchester, England)*. 15(40); pp 1–210

Staahl, C. and Drewes, A.J. 2004. Experimental human pain models: a review of standardised methods for preclinical testing of analgesics. *Basic and Clinical Pharmacology and Toxicology*. 95; pp 97-111

Starks, H. Brown Trinidad, S. 2007. Choose Your Method: A Comparison of Phenomenology, Discourse Analysis, and Grounded Theory. *Qualitative Health Research*. 17(10); pp 1372–1380

Stewart, K.J., Hiatt, W.R., Regensteiner, J.G., Hirsch, A.T. 2002. Review: medical progress: exercise therapy for claudication. *New England Journal of Medicine*. 347(24); pp 1941-1951

Streiner, D.L. and Norman, G.R. 2008. *Health Measurement Scales: A Practical Guide to Their Development and Use*. 4th ed. Oxford University Press, Oxford.

Strong, J. 1999. Assessment of pain perception in clinical practice. *Manual Therapy*. 4(4); pp 216-220

Sullivan, M.J.L., Bishop, S., Pivik, J. 1995. The Pain Catastrophizing Scale: development and validation. *Psychological Assessment*. 7; pp 524–32

Sullivan, M.J., Thorn, B., Haythornthwaite, J.A., Keefe, F., Martin, M., Bradley, L.A., Lefebvre, J.C. 2001. Theoretical perspectives on the relation between catastrophizing and pain. *The Clinical Journal of Pain*. 17(1); pp 52–64

Sullivan, M.J.L., Martel, M.O., Tripp, D., Savard, A., Crombez, G. 2006. The relation between catastrophizing and the communication of pain experience. *Pain*. 122(3); pp 282–288

Swinkels-Meewisse, I.E.J., Roelofs, J., Verbeek, A.L.M., Oostendorp, R.A.B., Vlaeyen, J.W.S. 2003. Fear of movement/(re)injury, disability and participation in acute low back pain. *Pain*. 105(1-2); pp 371–379

Sweers, I. 2007. An investigation into the hypoalgesic effects of Transcutaneous Electrical Nerve Stimulation (TENS) on experimentally induced ischaemia in the upper and lower limbs of the supine subject. Unpublished Observations. MSc Dissertation, Queen Margaret University

Szuba, A., Oka, R.K., Harada, R., Cooke, J.P. 2006. Limb hemodynamics are not predictive of functional capacity in patients with PAD. *Vascular Medicine*. 11(3); pp 155–163

Tashani, O.A. and Johnson, M.I. 2010. Avicenna's concept of pain. *Libyan Journal of Medicine*. 5(5253); pp 1-4

ter Riet, G., de Craen, A.J.M., de Boer, A., Kessels, A.G.H. 1998. Is placebo analgesia mediated by endogenous opioids? A systematic review. *Pain*. 76; pp 273–275

Thorne, S. 2008. *Interpretive description*. Walnut Creek, CA: Left Coast Press.

Thorne, S. 2011. Toward Methodological Emancipation in Applied Health Research. *Qualitative Health Research* 21(4); pp 443–453

Thorne, S., Reimer Kirkham, S., MacDonald-Emes, J. 1997. Interpretive description: A non-categorical qualitative alternative for developing nursing knowledge. *Research in Nursing & Health*. 20(2); pp 169-177

Todeschini, R., Consonni, V., Mauri, A., Pavan, M. 2004. Detecting ‘bad’ regression models: multicriteria fitness functions in regression analysis. *Analytica Chimica Acta*. 515(1); pp 199–208

Topliss, J.G. and Costello, R.J. 1972. Chance correlations in structure-activity studies using multiple regression analysis. *Journal of Medicinal Chemistry*. 15(10); pp 1066–1068

Tracey, I. and Bushnell, M.C. 2009. How Neuroimaging Studies Have Challenged Us to Rethink: Is Chronic Pain a Disease? *The Journal of Pain*. 10(11); pp 1113-1120

Treat-Jacobson, D., Halverson, S.L., Ratchford, A., Regensteiner, J.G., Lindquist, R., Hirsch, A. 2002. A patient-derived perspective of Health-Related Quality of Life with Peripheral Arterial Disease. *Journal of Nursing Scholarship*. 34(1); pp 55-60

Treat-Jacobson, D., Henly, S.J., Bronas, U.G., Leon, A.S., Henly, G.A. 2011. The pain trajectory during treadmill testing in peripheral artery disease. *Nursing Research*. 60(Supplement); pp S38–S49

Treede, R.D., Kenshalo, D.R., Gracely, R.H., Jones, A.K. 1999. The cortical representation of pain. *Pain*. 79(2-3); pp 105–111

Treesak, C., Kasemsup, V., Treat-Jacobson, D., Nyman, J.A., Hirsch, A.T. 2004. Cost-effectiveness of exercise training to improve claudication symptoms in patients with peripheral arterial disease. *Vascular Medicine*. 9(4); pp 279–285

Turk, D.C. and Monarch, E.S. 2002. Biopsychosocial perspective on chronic pain. In: Turk, D.C. and Gatchel, R. J. Eds. *Psychological approaches to pain management: A practitioner's handbook (2nd ed.)*. New York, NY, US: Guilford Press, pp 3–29

Tulgar, M., McGlone, F., Bowsher, D., Miles, J. 1991. Comparative effectiveness of different stimulation modes in relieving pain. Part II. A double-blind controlled long-term clinical trial. *Pain*. 47; pp 157-162

Turk, D.C., Rudy, T.E., Salovey, P. 1985. The McGill Pain Questionnaire reconsidered: confirming the factor structure and examining appropriate uses. *Pain*. 21; pp 385-397

Turner, J.A., Jensen, M.P., Romano, J.M. 2000. Do beliefs, coping, and catastrophising independently predict functioning in patients with chronic pain? *Pain*. 85; pp 115-125

Turner, J.A., Ersek, M., Kemp, C. 2005. Self-efficacy for managing pain is associated with disability, depression, and pain coping among retirement community residents with chronic pain. *The Journal of Pain*. 6(7); pp 471–479

Vance, C.G.T., Rakel, B.A., Blodgett, N.P., DeSantana, J.M., Amendola, A., Zimmerman, M.B., Walsh, D.M., Sluka, K.A. 2012. Effects of transcutaneous electrical nerve stimulation on pain, pain sensitivity, and function in people with knee osteoarthritis: a randomized controlled trial. *Physical Therapy*. 92(7); pp 898–910

Vancleef, L.M.G. and Peters, M.L. 2011. The influence of perceived control and self-efficacy on the sensory evaluation of experimentally induced pain. *Journal of Behavior Therapy and Experimental Psychiatry*. 42(4); pp 511–517

van Damme, S., Crombez, G., Bijttebier, P., Goubert, L., van Houdenhove, B., 2002. A confirmatory factor analysis of the Pain Catastrophizing Scale: invariant factor structure across clinical and non-clinical populations. *Pain*. 96, pp 319-324

van Wijk, A. and Hoogstraten, J. 2002. The McGill Pain Questionnaire in dentistry: dental pain described in numbers. *Pain Reviews*. 9(2); pp 87-97

Vetter, T.R. 2007. A primer on health-related quality of life in chronic pain medicine. *Anesthesia & Analgesia*. 104(3); pp 703-718

Villemure, C. and Bushnell, M. 2002. Cognitive modulation of pain: how do attention and emotion influence pain processing? *Pain*. 95; pp 195-199.

Vlaeyen, J.W.S., Kole-Snijders, A.M.J., Boeren, R.G.B., van Eek, H. 1995. Fear of movement/(re) injury in chronic low back pain and its relation to behavioural performance. *Pain*. 62; pp 363-372

Waddell, G., Newton, M., Henderson, I., Somerville, D., Main, C.J. 1993. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. *Pain*. 52(2); pp 157–168

Wall, P.D. and Sweet, W.H. 1967. Temporary abolition of pain in man. *Science*. 155; pp 108-109

Walsh, D. 1997. *TENS. Clinical Applications and Related Theory*. Churchill Livingstone, New York.

Walsh, D.M., Liggett, C., Baxter, D., Allen, J.M. 1995a. A double-blind investigation of the hypoalgesic effects of transcutaneous electrical nerve stimulation upon experimentally induced ischaemic pain. *Pain*. 61(1); pp 39-40

Walsh, D.M.D., Foster, N.E.N., Baxter, G.D.G., Allen, J.M.J. 1995b. Transcutaneous electrical nerve stimulation. Relevance of stimulation parameters to neurophysiological and hypoalgesic effects. *American Journal of Physical Medicine & Rehabilitation*. 74(3), pp. 199–206

Walsh, D.M., Howe, T.E., Johnson, M.I., Sluka, K.A. 2009. Transcutaneous electrical nerve stimulation for acute pain. *Cochrane Database of Systematic Reviews* Issue 2. pp CD006142.

Wann-Hansson, C., Hallberg, I.R., Klevsgard, R., Andersson, E, 2005. Patients' experiences of living with peripheral arterial disease awaiting intervention: a qualitative study. *International Journal of Nursing Studies*. 42; pp 851-862

Wann-Hansson, C., Hallberg, I.R., Klevsgard, R., Andersson, E. 2008. The long-term experience of living with peripheral arterial disease and the recovery following revascularisation: A qualitative study. *International Journal of Nursing Studies*. 45; pp 552-561

Wannamethee, S.G. and Shaper, A.G. 2001. Physical activity in the prevention of cardiovascular disease: an epidemiological perspective. *Sports Medicine*. 31(2); pp 101-114

World Health Organisation (WHO) 2005. Handbook for good clinical research practice (GCP): guidance for implementation. WHO Library, France. ISBN 92 4 159392 X. Available Online: [http://whqlibdoc.who.int/publications/2005/924159392X\\_eng.pdf](http://whqlibdoc.who.int/publications/2005/924159392X_eng.pdf) [Accessed 20/01/2013]

White, C.J. and Gray, W.A. 2007. Endovascular Therapies for Peripheral Arterial Disease: An Evidence-Based Review. *Circulation*. 116; pp 2203-2215

Wiech, K., Ploner, M., Tracey, I. 2008. Neurocognitive aspects of pain perception. *Trends in Cognitive Sciences*. 12(8); pp 306-313

Wilkie, D.J., Saverda, M.C., Holzemier, W.L., Tesler, M.D., Paul, S.M. 1990. Use of the McGill Pain Questionnaire to measure pain: A meta-analysis. *Nursing Research*. 39; pp 36-41

Wilkie, D.J., Huang, H.Y., Reilly, N., Cain, K.C. 2001. Nociceptive and neuropathic pain in patients with lung cancer: a comparison of pain quality descriptors. *Journal of Pain and Symptom Management*. 22(5); pp 899–910

Wilkinson, S. 1998. Focus groups in health research: exploring the meanings of health and illness. *Journal of Health Psychology*. 3(3); pp 329-348



- Williams, M.V., Baker, D.W., Parker, R.M., Nurss, J.R. 1998. Relationship of functional health literacy to patients' knowledge of their chronic disease. A study of patients with hypertension and diabetes. *Archives of Internal Medicine*. 158(2); pp 166–172
- Williamson, A. and Hoggart, B. 2005. Pain: a review of three commonly used pain rating scales. *Journal of Clinical Nursing*. 14(7); pp 798–804
- Wills, T.A. 1981. Downward comparison principles in social psychology. *Psychological Bulletin*. 90(2); pp 245-271
- Woby, S.R., Urmston, M., Watson, P.J. 2007. Self-efficacy mediates the relation between pain-related fear and outcome in chronic low back pain patients. *European Journal of Pain*. 11(7); pp 711–718
- Wong, E.M.-L., Chan, S.W.-C., Chair, S.-Y. 2010. Effectiveness of an educational intervention on levels of pain, anxiety and self-efficacy for patients with musculoskeletal trauma. *Journal of Advanced Nursing*. 66(5); pp 1120–1131
- Woolf, C.J. 1979. Transcutaneous electrical nerve stimulation and the reaction to experimental pain in human subjects. *Pain*. 7(2); pp 115-127
- Woolf, C. and Thompson, J. 1994. Segmental afferent fibre-induced analgesia: transcutaneous electrical nerve stimulation (TENS) and vibration. In: Wall P, Melzack R, (Ed). *Textbook of pain*. Edinburgh: Churchill Livingstone. pp 1191–208
- Wright, K.D., Asmundson, G.J.G., McCreary, D.R. 2001. Factorial validity of the short-form McGill pain questionnaire (SF-MPQ). *European Journal of Pain*. 5; pp 279-284.
- Yusuf, S., Sleight, P., Pogue, J., Bosch, J., Davies, R., Dagenais, G. 2000. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in highrisk patients. The heart outcomes prevention evaluation study investigators. *New England Journal of Medicine*. 342(3); pp 145-153
- Yusuf, S., Hawken, S., Ounpuu, S. 2005. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet*. 366; pp 1640-1649
- Zierath, J.R. and Hawley, J.A. 2004. Skeletal muscle fiber type: influence on contractile and metabolic properties. *PLoS Biology*. 2(10); pp e348

## CHAPTER 14:APPENDICES

### 14.1: APPENDIX 1: DETAILS OF SEARCH RESULTS AND REASONS FOR EXCLUSION

Author(s)	Year	Reason for Exclusion
Hughes et al	2013	Pain not main outcome
Venancio et al	2013	Pain not main outcome
Atamaz et al	2012	Not Ischaemic pain
Kim et al	2012	Not Ischaemic pain
Kolen et al	2012	Not Ischaemic pain
Mulvey et al	2012	Not Ischaemic pain
Rocha et al	2012	Not Ischaemic pain
Dounavi et al	2012	Not TENS
Casale et al	2012	Review
Racine et al	2012	Review
Veening et al	2012	Review
Aelik et al	2011	Not Ischaemic pain
Amer-Cuenca et al	2011	Not Ischaemic pain
Facci et al	2011	Not Ischaemic pain
Francis et al	2011	Not Ischaemic pain
Fuentes et al	2011	Not Ischaemic pain
Moran et al	2011	Not Ischaemic pain
Pantalealo et al	2011	Not Ischaemic pain
Choi et al	2011	Not TENS
e Silva et al	2011	Not TENS
Kumar and Saha	2011	Not TENS
Pereira et al	2011	Not TENS
Tronnier et al	2011	Not TENS
Shipshina et al	2011	Pain not main outcome
Claydon et al	2011	Review
Francis and, Johnson	2011	Review
Johnson and Bjordal	2011	Review
Plastaras et al	2011	Review
Bennett et al	2010	Not Ischaemic pain
Chen and Johnson	2010	Not Ischaemic pain
Hallen et al	2010	Not Ischaemic pain
Kavak et al	2010	Not Ischaemic pain
Rodrigues et al	2010	Not Ischaemic pain
Fralich	2010	Not TENS
Jorge Fuentes et al	2010	Not TENS
Rossini et al	2010	Not TENS
Hallan et al	2010	Pain not main outcome
Jelinek et al	2010	Pain not main outcome
Amer-Cuenca et al	2010	Review
Fuentes et al	2010	Review
Hashmi et al	2010	Review
Huang and Yu	2010	Review

---

Kones	2010	Review
Mekhail et al	2010	Review
Amer-Cuenca	2010	Short Survey
Martins et al	2009	Conference Paper
Adedoyin et al	2009	Not Ischaemic pain
Chen and Johnson	2009	Not Ischaemic pain
Cowan et al	2009	Not Ischaemic pain
DeSantana et al	2009	Not Ischaemic pain
Dickie et al	2009	Not Ischaemic pain
Helmers et al	2009	Not Ischaemic pain
Tuveson et al	2009	Not Ischaemic pain
Ward et al	2009	Not Ischaemic pain
Ward et al	2009	Not Ischaemic pain
Bolfe and Guirro	2009	Not TENS
Butler and Finn	2009	Review
Deer	2009	Review
Jeon and Huh	2009	Review
Salinas Bueno et al	2009	Review
Qin et al	2008	Not humans
Sharifi et al	2008	Not humans
Burch et al	2008	Not Ischaemic pain
Claydon et al	2008	Not Ischaemic pain
Satter	2008	Not Ischaemic pain
Davis et al	2008	Pain not main outcome
Maciel et al	2008	Pain not main outcome
Chen et al	2008	Review
DeSantana et al	2008	Review
Jenrich	2008	Review
White et al	2008	Review
Chesterton et al	2007	Not Ischaemic pain
Edwards et al	2007	Not Ischaemic pain
Goroszeniuk et al	2007	Not Ischaemic pain
Shimoji et al	2007	Not Ischaemic pain
Tong et al	2007	Not Ischaemic pain
Tugay et al	2007	Not Ischaemic pain
Tuveson et al	2007	Not Ischaemic pain
Zambito et al	2007	Not Ischaemic pain
De Andras et al	2007	Not TENS
Peters and George	2007	Not TENS
Gold et al	2007	Pain not main outcome
Foletti et al	2007	Review
Dean et al	2006	Not Ischaemic pain
Shanahan et al	2006	Not Ischaemic pain
Zambito et al	2006	Not Ischaemic pain
Buchser et al	2006	Not TENS
Jorge et al	2006	Not TENS
Limansky et al	2006	Not TENS

---

Tuveson et al	2006	Not TENS
Allen	2006	Review
Deer and Raso	2006	Review
Gur	2006	Review
Hoskins and Pollard	2005	Not Ischaemic pain
Kavcic et al	2005	Not Ischaemic pain
Adedoyin et al	2005	Not TENS
Apkarian et al	2005	Not TENS
Palmer et al	2004	Not Ischaemic pain
Schubert et al	2004	Not Ischaemic pain
Briggs et al	2004	Not TENS
Segerdahl and Karelov	2004	Not TENS
Tripp et al	2004	Not TENS
Martin et al	2004	Pain not main outcome
Akkaya and Sayin	2004	Review
Cameron	2004	Review
Dolan and Mendel	2004	Review
Kavuncu and Evcik	2004	Review
Chesterton et al	2003	Not Ischaemic pain
Johnson and Tabasam	2003	Not Ischaemic pain
Johnson et al	2003	Not Ischaemic pain
Roche et al	2003	Not Ischaemic pain
Haas et al	2002	Not Ischaemic pain
Leffler et al	2002	Not Ischaemic pain
Johnson and Tabasam	2002	Not TENS
Roche et al	2002	Not TENS
Campbell and Ditto	2002	Pain not main outcome
Borjesson and Norrsell	2001	Review
Johnson	2001	Review
Latif et al	2001	Review
Naslund	2001	Review
White et al	2001	Review
Kosek et al	2000	Not Ischaemic pain
Norrsell et al	2000	Not Ischaemic pain
Presser et al	2000	Not Ischaemic pain
Barlas et al	2000	Not TENS
Eriksson et al	2000	Not TENS
Blond	2000	Review
Johnson	2000	Review
Gracely	1999	Conference Paper
Johnson and Tasbam	1999	Conference Paper
Sluka et al	1999	Conference Paper
Borjesson	1999	Not Ischaemic pain
Börjesson and Herz	1999	Not Ischaemic pain
Ghophone et al	1999	Not Ischaemic pain
Hamza et al	1999	Not Ischaemic pain
Johnson and Tabasam	1999	Not Ischaemic pain

McDowell et al	1999	Not Ischaemic pain
McDowell et al	1999	Not Ischaemic pain
Svensson et al	1999	Not Ischaemic pain
Talley	1999	Not Ischaemic pain
Ghonaime et al	1999	Not TENS
McDowell et al	1999	Not TENS
Palmer et al	1999	Pain not main outcome
Borjesson	1999	Review
Segerdahl	1998	Conference Paper
Danziger et al	1998	Not Ischaemic pain
Sawynok	1998	Pain not main outcome
Kumar et al	1998	Review
Sawynok	1998	Review
Sandkahler et al	1997	Not humans
Hardy and Hardy	1997	Not Ischaemic pain
Kosek et al	1997	Not Ischaemic pain
Towell et al	1997	Not Ischaemic pain
Lowe et al	1997	Not TENS
Wilson	1997	Not TENS
Stanton-Hicks and Salamon	1997	Review
Sylvan	1997	Review
Brochet	1996	Not English
Craig et al	1996	Not Ischaemic pain
Robinson	1996	Not Ischaemic pain
McDowell et al	1996	Not TENS
Sylvan	1996	Not TENS
Eliasson et al	1996	Review
Hautvast et al	1996	Review
Robinson	1996	Review
Cristal et al	1994	Not Ischaemic pain
Kemppainen and Petovaara	1987	Not Ischaemic pain
Chen and Johnson	2011	
Brown et al	2007	
Johnson and Tasbam	2003	
Foster et al	1996	
Walsh et al	1995	
Roche et al	1984	
Rosenblatt and Hetherington	1981	
Woolf	1979	

## 14.2: APPENDIX 2: STANDARDISED DATA EXTRACTION TABLES

<b>Study:</b>	<b>Rosenblatt and Hetherington 1981, Anesthesia and Analgesia</b>
<b>Study aim:</b>	Evaluate the effectiveness of TENS to alleviate upper limb tourniquet pain as clinically encountered in anaesthesia
<b>Methods</b>	
<b>Design:</b>	Repeated measures, cross-over design
<b>Outcome measures:</b>	Time to pain tolerance Pain intensity measured by a VAS after deflation of the tourniquet
<b>Blinding:</b>	None
<b>TENS administered by:</b>	Researcher
<b>Participants</b>	
<b>No of participants randomized:</b>	10
<b>Male/female:</b>	8/2
<b>Mean age:</b>	29.8 years
<b>Intervention:</b>	
<b>Type of ischaemic pain:</b>	UL SETT (25 mins, 250, 20x30lb)
<b>No of conditions (list)</b>	Control Single channel TENS Dual channel TENS
<b>No per group:</b>	10 (crossover)
<b>TENS device:</b>	Medgeneral Miniceptor II
<b>Frequency:</b>	100Hz
<b>Intensity:</b>	Maximum tolerated
<b>Pulse duration:</b>	40µsec
<b>Electrodes (dimensions, no and placement):</b>	Dimensions not specified 2 electrodes Single: One placed proximal to cuff over axillary artery and the other opposite circumferentially Dual: extra 2 electrodes in spaces between
<b>Stimulation duration:</b>	Throughout
<b>Monitoring duration:</b>	Throughout
<b>Placebo group methods, control group methods:</b>	No Placebo Control = no TENS
<b>Outcomes:</b>	
<b>Who took the measurement? Were they blinded?</b>	The researcher
<b>Time interval between each measurement:</b>	None- one-of measurement

<b>Total number of measures taken:</b>	1
<b>Statistical test(s) used:</b>	Student's t-test
<b>Results</b>	
<b>Main results:</b>	No difference in time to pain tolerance No difference in Pain intensity
<b>Authors conclusion regarding outcome:</b>	TENS has no effect on ischaemic pain. TENS is therefore ineffective analgesia for tourniquet pain.
<b>Reviewers conclusion regarding outcome:</b>	Very small numbers and questionable TENS technique. No statistical test data reported Looking for analgesia rather than hypoalgesia Poor TENS technique and settings

<b>Study:</b>	<b>Roche et al 1984, Pain</b>
<b>Study aim:</b>	Record the differences in response of healthy subjects to ischaemic pain when treated with TENS
<b>Methods</b>	
<b>Design:</b>	RCT
<b>Outcome measures:</b>	Time to pain threshold Time to pain tolerance Pain endurance VAS PPI MPQ
<b>Blinding:</b>	None
<b>TENS administered by:</b>	Researcher
<b>Participants</b>	
<b>No of participants randomized:</b>	48
<b>Male/female:</b>	24/24
<b>Mean age:</b>	24
<b>Intervention</b>	
<b>Type of ischaemic pain:</b>	UL SETT (25 mins, 250, 20xmax grip strength)
<b>No of conditions (list)</b>	1. No TENS control 2. HF/HI TENS 3. LF/HI TENS 4. LF/LI TENS
<b>No per group:</b>	12 (6/6)
<b>TENS device:</b>	'Square pulse generator'
<b>Frequency:</b>	1. None 2. 100Hz 3. 5Hz 4. 5Hz
<b>Intensity:</b>	1. None

	2. Maximum tolerated 3. Maximum tolerated 4. Perceptible prickling sensation
<b>Pulse duration:</b>	1. None 2. 1msec 3. 100msec 4. 100msec
<b>Electrodes (dimensions, no and placement):</b>	2x2cm, 2 electrodes, RU Joint and Cubital fossa
<b>Stimulation duration:</b>	10 mins prior to SETT and throughout
<b>Monitoring duration:</b>	None post SETT
<b>Placebo group methods, control group methods:</b>	No stimulation, just SETT
<b>Outcomes:</b>	
<b>Who took the measurement? Were they blinded?</b>	Researcher, not blind
<b>Time interval between each measurement:</b>	VAS = 1 minute MPQ= NA
<b>Total number of measures taken:</b>	Max 25
<b>Statistical test(s) used:</b>	Student's t-test Pearson's correlation coefficient
<b>Results</b>	
<b>Main results:</b>	LF/LI TENS increase time to threshold greater than control HF/HI TENS and LF/LI TENS increase time to tolerance greater than control HF/HI TENS increase endurance time greater than control VAS scores correlated with PPI throughout HF/HI TENS decrease MPQ-PRI scores greater than control for all aspects and NWC
<b>Authors conclusion regarding outcome:</b>	High and low intensity TENS increases time to tolerance Low intensity increases time to perceive pain High intensity increases endurance time SETT induced comparable pain
<b>Reviewers conclusion regarding outcome:</b>	Poor design and analysis of data No repeated measures or attempt to quantify differences in groups Limited stats testing TENS may have effect but parameters chosen ineffective.

<b>Study:</b>	<b>Walsh et al 1995a, Pain</b>
---------------	--------------------------------



<b>Study aim:</b>	Compare the effects of high and low frequency TENS on experimental pain using the SETT
<b>Methods</b>	
<b>Design:</b>	Repeated measures, RCT with placebo and control
<b>Outcome measures:</b>	VAS at time every minute throughout SF-MPQ for 'worst pain'
<b>Blinding:</b>	Double-blinded
<b>TENS administered by:</b>	Independent researcher
<b>Participants</b>	
<b>No of participants randomized:</b>	32
<b>Male/female:</b>	0/32
<b>Mean age:</b>	Not stated
<b>Intervention</b>	
<b>Type of ischaemic pain:</b>	UL SETT (12 mins, ND, 200, 20x75%Max Grip)
<b>No of conditions (list)</b>	1. Control 2. Placebo 3. HF-TENS 4. LF-TENS
<b>No per group:</b>	8
<b>TENS device:</b>	Tensaid (Hong Kong) commercial machine
<b>Frequency:</b>	1. None 2. None (not active) 3. 110Hz 4. 4Hz
<b>Intensity:</b>	1. None 2. 'Midway' (participant controlled after this point) 3. Strong but comfortable (participant controlled throughout) 4. Strong but comfortable and visible muscle contractions (participant controlled throughout)
<b>Pulse duration:</b>	287 $\mu$ sec
<b>Electrodes (dimensions, no and placement):</b>	2 inch self-adhesive PALS Erb's point (over brachial plexus between sternocleidomastoid and clavicle) and just lateral to C6 and C7 on non-dominant side
<b>Stimulation duration:</b>	10 mins prior to cuff inflation and throughout test (12 mins)
<b>Monitoring duration:</b>	None post-SETT
<b>Placebo group methods, control group methods:</b>	All participants were told that they may experience sensations with TENS. Placebo group TENS was not connected to an active socket but they were encouraged to alter intensity
<b>Outcomes:</b>	
<b>Who took the</b>	Researcher who was blinded to type of TENS, not

<b>measurement? Were they blinded?</b>	intervention
<b>Time interval between each measurement:</b>	1 minute VAS MPQ at 'conclusion of testing'
<b>Total number of measures taken:</b>	12 VAS 1 MPQ
<b>Statistical test(s) used:</b>	One-way and repeated measures ANOVA and post-hoc tests
<b>Results</b>	
<b>Main results:</b>	Mean VAS reduced with LF-TENS compared to Control and HF-TENS Mean VAS reduced with Placebo TENS compared to HF-TENS VAS with LF-TENS decreased to a greater extent than all other groups in minutes 7-9 VAS with LF-TENS decreased to a greater extent than control and HF-TENS in 4 <sup>th</sup> minute No significant differences were observed in MPQ-PRI scores
<b>Authors conclusion regarding outcome:</b>	TENS reduces ischaemic pain LF more effective than HF-TENS Appears that the extrasegmental pathways that LF-TENS is proposed to work at do not hold for these results
<b>Reviewers conclusion regarding outcome:</b>	Well conducted and double-blind study Sufficient TENS parameters used Good analysis and robust statistics No randomisation of the conditions- participants likely to reduce their ratings of pain as they are more used to the stimulation TENS switched on 10 mins prior to pain induction thus allowing LF-TENS effects to take hold?

<b>Study:</b>	<b>Foster et al 1996, Clinical Journal of Pain</b>
<b>Study aim:</b>	Assess the hypoalgesic effects of changing TENS parameters on cold and ischaemic pain in healthy volunteers
<b>Methods</b>	
<b>Design:</b>	Repeated measures, RCT, Placebo, Control and 4 TENS conditions
<b>Outcome measures:</b>	VAS MPQ
<b>Blinding:</b>	Double-blinded
<b>TENS administered by:</b>	Independent researcher
<b>Participants</b>	
<b>No of participants randomized:</b>	48
<b>Male/female:</b>	24/24

<b>Mean age:</b>	19.4 years
<b>Intervention</b>	
<b>Type of ischaemic pain:</b>	ND UL SETT (12 mins, 200, 20x75%Max Grip, 13cm)
<b>No of conditions (list)</b>	<ol style="list-style-type: none"> <li>1. HF-TENS / Long Pulse Duration</li> <li>2. HF-TENS / Short Pulse Duration</li> <li>3. LF-TENS / Short Pulse Duration</li> <li>4. LF-TENS / Long Pulse Duration</li> <li>5. Placebo</li> <li>6. Control</li> </ol>
<b>No per group:</b>	8
<b>TENS device:</b>	120Z TENS unit (ITO Tokyo)
<b>Frequency:</b>	<ol style="list-style-type: none"> <li>1. 110Hz</li> <li>2. 110Hz</li> <li>3. 4Hz</li> <li>4. 4HZ</li> <li>5. None</li> <li>6. None</li> </ol>
<b>Intensity:</b>	<ol style="list-style-type: none"> <li>1. Strong but comfortable</li> <li>2. Strong but comfortable</li> <li>3. Strong but comfortable</li> <li>4. Strong but comfortable</li> <li>5. None</li> <li>6. None</li> </ol>
<b>Pulse duration:</b>	<ol style="list-style-type: none"> <li>1. 200 <math>\mu</math>sec</li> <li>2. 50 <math>\mu</math>sec</li> <li>3. 50 <math>\mu</math>sec</li> <li>4. 200 <math>\mu</math>sec</li> <li>5. None</li> <li>6. None</li> </ol>
<b>Electrodes (dimensions, no and placement):</b>	<p>Two carbon rubber electrodes with hydrogel pads 3.5 x 5cm</p> <p>Lateral to the spinous processes of C6 and C7 and Erb's point</p>
<b>Stimulation duration:</b>	<p>23 mins prior to cuff inflation</p> <p>Switched off for 2 mins of SETT induction</p> <p>Back on for the rest</p>
<b>Monitoring duration:</b>	None
<b>Placebo group methods, control group methods:</b>	<p>May or may not experience sensation from TENS</p> <p>Electrodes placed but attached to a non-active socket</p> <p>Control just same as baseline</p>
<b>Outcomes:</b>	
<b>Who took the measurement? Were they blinded?</b>	Researcher, blinded to TENS type
<b>Time interval between each</b>	VAS = 1 minute

<b>measurement:</b>	MPQ = NA
<b>Total number of measures taken:</b>	VAS = 12 MPQ = 1
<b>Statistical test(s) used:</b>	Used difference scores as a means of standardisation for inter-subject variability (Intervention score – Baseline) ANOVA
<b>Results</b>	
<b>Main results:</b>	No significant differences in VAS or MPQ scores between groups or over time
<b>Authors conclusion regarding outcome:</b>	Selected pulse durations have little effect but longer durations (Walsh et al 1995a- 287 $\mu$ sec) have shown effectiveness. Electrode placement sites not good- needs to be over the site of pain Intensity not strong enough.
<b>Reviewers conclusion regarding outcome:</b>	Insufficient TENS parameters used- pulse duration, electrode placement, time of stimulation Same issues as Walsh et al 1995a in terms of design with no randomisation of enter into conditions Good double blinding and statistical analysis Repeated measures strong and even better to use difference scores

<b>Study:</b>	<b>Johnson and Tasbasam 2003, Physical Therapy</b>
<b>Study aim:</b>	Compared the analgesic effects of TENS and IF on ischaemic pain in healthy volunteers
<b>Methods</b>	
<b>Design:</b>	Single-blind, placebo-controlled repeated measures experiment
<b>Outcome measures:</b>	VAS every minute SF-MPQ
<b>Blinding:</b>	Participant blinded to treatment type
<b>TENS administered by:</b>	Researcher
<b>Participants</b>	
<b>No of participants randomized:</b>	30
<b>Male/female:</b>	18/12
<b>Mean age:</b>	33.5 years
<b>Intervention</b>	
<b>Type of ischaemic pain:</b>	SETT (12 mins, 200, forearm, 20x75%Maxgrip) Cuff inflation = 0
<b>No of conditions (list)</b>	1. IFC 2. TENS

	3. Placebo
<b>No per group:</b>	10
<b>TENS device:</b>	EMS model 70 interferential therapy machine
<b>Frequency:</b>	1. 100Hz x 4kHz 2. 100Hz 3. None
<b>Intensity:</b>	1. Strong but comfortable and participant controlled 2. Strong but comfortable and participant controlled 3. None
<b>Pulse duration:</b>	1. NA 2. 200 µsec 3. None
<b>Electrodes (dimensions, no and placement):</b>	4, self-adhesive 4.5cm <sup>2</sup> electrodes, 2 below, 2 above cuff on anterior and posterior forearm
<b>Stimulation duration:</b>	22 mins uninterrupted
<b>Monitoring duration:</b>	None post SETT
<b>Placebo group methods, control group methods:</b>	Same machine, attached to non-active socket Same electrode placement and instructions that they may or may not experience sensations Post-test questionnaire proved placebo effective for all participants
<b>Outcomes:</b>	
<b>Who took the measurement? Were they blinded?</b>	Researcher not blinded
<b>Time interval between each measurement:</b>	VAS = 1 minute MPQ = NA
<b>Total number of measures taken:</b>	VAS = 12 SF-MPQ = 1
<b>Statistical test(s) used:</b>	Analysed change scores for VAS and MPQ Two-way repeated measures ANOVA for VAS One-way ANOVA for MPQ
<b>Results</b>	
<b>Main results:</b>	No difference in VAS scores with TENS from control or placebo No difference in the change in SF-MPQ scores between the groups
<b>Authors conclusion regarding outcome:</b>	TENS is ineffective at reducing ischaemic pain and no better than IFC however, this may be due to the parameters used
<b>Reviewers conclusion regarding outcome:</b>	Different type of SETT with cuff on forearm Again no randomisation of entry into conditions which may affect results- decrease due to fear of increase due to familiarisation Increased due to concept and expectation of an

	<p>'intervention'</p> <p>Good statistics used</p> <p>Electrode placement over pain but mechanical pain rather than ischaemic?</p>
--	---

<b>Study:</b>	<b>Chen and Johnson 2011, Clinical Journal of Pain</b>
<b>Study aim:</b>	Assess the effects of LF and HF-TENS on ischaemic pain in healthy volunteers
<b>Methods</b>	
<b>Design:</b>	Repeated measures, placebo-controlled, cross-over
<b>Outcome measures:</b>	VAS SF-MPQ
<b>Blinding:</b>	Double blind to type of TENS
<b>TENS administered by:</b>	Independent researcher
<b>Participants</b>	
<b>No of participants randomized:</b>	48
<b>Male/female:</b>	24/24
<b>Mean age:</b>	26.8 years
<b>Intervention</b>	
<b>Type of ischaemic pain:</b>	Familiarisation session then 3 x Forearm SETT (200, 15 x 75% MGS, 2 mins duration) with 30 mins washout
<b>No of conditions (list)</b>	<ol style="list-style-type: none"> <li>1. LF-TENS</li> <li>2. HF-TENS</li> <li>3. Placebo</li> <li>4. Baseline</li> </ol>
<b>No per group:</b>	<p>N = 8</p> <ol style="list-style-type: none"> <li>1. LF-TENS / HF-TENS / Placebo</li> <li>2. LF-TENS / Placebo / HF-TENS</li> <li>3. HF-TENS / Placebo / LF-TENS</li> <li>4. HF-TENS / LF-TENS / Placebo</li> <li>5. Placebo / LF-TENS / HF-TENS</li> <li>6. Placebo / HF-TENS / LF-TENS</li> </ol>
<b>TENS device:</b>	Pro-TENS Nidd Valley Medical Limited UK
<b>Frequency:</b>	<ol style="list-style-type: none"> <li>1. 3Hz</li> <li>2. 80Hz</li> <li>3. None</li> </ol>
<b>Intensity:</b>	<ol style="list-style-type: none"> <li>1. Strong but comfortable</li> <li>2. Strong but comfortable</li> <li>3. None</li> </ol>
<b>Pulse duration:</b>	<ol style="list-style-type: none"> <li>1. 200 <math>\mu</math>sec</li> <li>2. 200 <math>\mu</math>sec</li> <li>3. None</li> </ol>
<b>Electrodes (dimensions, no</b>	Midline of anterior and posterior forearm both sides of cuff

<b>and placement):</b>	Self-adhesive 5x5cm
<b>Stimulation duration:</b>	20 mins- SETT in last 5 mins of stimulation
<b>Monitoring duration:</b>	None post SETT
<b>Placebo group methods, control group methods:</b>	No current output but indicator light on for placebo
<b>Outcomes:</b>	
<b>Who took the measurement? Were they blinded?</b>	Researcher was blinded
<b>Time interval between each measurement:</b>	VAS = 1 minute MPQ = NA
<b>Total number of measures taken:</b>	VAS = 2 SF-MPQ = 1
<b>Statistical test(s) used:</b>	2x4 factorial repeated measures ANOVA on VAS data Repeated measures ANOVA for MPQ-PRI scores with Bonferroni correction
<b>Results</b>	
<b>Main results:</b>	<p>HF-TENS reduced VAS scores compared to LF-TENS</p> <p>Significant effects of time and condition</p> <p>Baseline VAS lower than with placebo</p> <p>VAS with HF-TENS lower than with placebo</p> <p>VAS scores with LF-TENS were higher than placebo</p> <p>Significant effects of condition in MPQ scores</p> <p>Lower SPRI scores at baseline than with placebo and LF-TENS</p> <p>Both TENS reduced SPRI compared to placebo</p> <p>No difference between TENS groups</p> <p>PPI significant effect for condition</p> <p>Baseline PPI scores were lower than in all other conditions</p> <p>Lower PPI with both TENS compared to placebo</p> <p>No differences between TENS for PPI</p>
<b>Authors conclusion regarding outcome:</b>	HF-TENS is more effective than LF-TENS for induced ischaemic pain although both reduced intensity compared to placebo
<b>Reviewers conclusion regarding outcome:</b>	<p>Excellent paper that comprehensibly compares LF and HF-TENS for ischaemic pain</p> <p>Different SETT method used but seems to induce ischaemic pain</p> <p>Talking about the interaction of stimulation and pain increasing sensory input is interesting</p> <p>Comprehensive statistics employed and described</p> <p>Double blind as well and mixed entry of conditions which improves validity</p> <p>Short period of ischaemic pain doesn't allow much analysis of development</p>

	<p>TENS on for a long period before SETT- this affects mechanisms at play?</p> <p>Interesting discussion of TENS affecting affective rather than sensory aspects of pain.</p>
--	---



### 14.3: APPENDIX 3: MODIFIED JADAD SCALE

**TABLE 1.** List of Criteria for Assessment of the Quality of Trials in the Review

<b>Randomization</b>	
1) Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?	Y/N (1 point/0 point)
2) The method to generate the sequence of randomization was described and it was appropriate (table of random numbers, computer generated, not date of birth, date of admission, hospital numbers, and alternation)?	Y/N (1 point/0 point)
<b>Blinding</b>	
3) Was the study described as double blind?	Y/N (1 point/0 point)
4) The method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy, or statement that neither the persons doing the assessments nor the study participants could identify the intervention being assessed)?	Y/N (1 point/0 point)
<b>Withdrawals and dropouts</b>	
5) Was there a description of withdrawals and dropouts? (The number and reasons for withdrawal in each group must be stated. If there were no withdrawals it should be stated in the article)	Y/N (1 point/0 point)
<b>Statistical power</b>	
Was there enough (80%) statistical power to detect a “large” ( $\geq 0.8$ ) pair-wise effect at a 2-tailed $\alpha$ of 0.05 ( $n = 26$ per group) (Cohen 1992) <sup>15</sup>	Y/N (1 point/0 point)
Scoring for the Jadad Scale: items 1 + 2 + 3 + 4 + 5 = 5 possible points; 0-2 = low quality and 3-5 = high quality. In the modified scale, item 5 is omitted and replaced with the statistical power item; 0-2 = low quality and 3-5 = high quality. N indicates no; Y, yes.	

Modified Jadad scale form Claydon et al (2011).



## Queen Margaret University EDINBURGH

This study has ethical approval

### INFORMATION SHEET

My name is Chris Seenan and I am a PhD student from the School of Health Sciences at Queen Margaret University in Edinburgh. As part of my degree course, I am undertaking a research project.

The title of my project is:

#### **Laboratory and clinical investigation into lower limb ischaemic pain, and the effect of Transcutaneous Electrical Nerve Stimulation (TENS) on measures of pain and exercise performance**

This study will investigate the effects of temporary ischaemia in the leg. Ischaemia occurs when there is a lack of blood supply to certain tissues. This is sometimes associated with a pain in the region of the calf. The pain is a common problem for patients with Peripheral Arterial Disease (PAD) and is brought on by exercise e.g. walking. It is not an indication of tissue damage, rather it is a brief period of pain which patients experience daily and resolves immediately without after effects. In this study we plan to briefly induce and investigate ischaemia in the calf.

There are two main aims of my study. The first is to compare the description of any pain resulting from ischaemia induced in healthy volunteers with that experienced by patients with PAD. The second aim is to investigate the effect of a commonly used physiotherapy treatment called Transcutaneous Electrical Nerve Stimulation (TENS) on any pain temporarily produced in the leg; along with treadmill walking performance in patients with PAD.

The findings of the project will improve the understanding of ischaemic pain and how it affects exercise and performance. TENS results will be considered as a possible cost-effective treatment for these patients, potentially improving their walking, exercise performance and quality of life.

I am looking for volunteers to participate in the project. Anyone can volunteer. However, there are strict inclusion and exclusion criteria that will be checked prior to testing. These are followed to ensure the safety and suitability of every subject participating in the project. Anyone with a history of DVT or clotting abnormalities will be excluded from participating. Screening of DVT risk factors will be completed prior to testing and cardiovascular markers will be monitored closely throughout testing. Also, prior to participating in the study, your heart rate and blood pressure will be measured. If these are found to be outwith normal limits, you will be informed of this result and will not be included in the study. I will also provide you with a letter of any abnormal findings to take to your general practitioner, who will advise you of the medical aspects and implications of this finding. If you do not have a general practitioner, I will instruct you on the steps to register with a practice via NHS 24 or provide information about contacting the university nurse.

If you are suitable to participate and you agree to take part in the study, you will be asked to attend for one testing session that will last for approximately 1 ½ hours. The procedure will involve completing a few short questionnaires and performing 20 gentle heel-raising exercises with a blood pressure cuff inflated around your thigh. You will be asked to do this twice with a rest period of 20 minutes between trials.

You are likely to experience pain during testing. If you do develop pain, it is expected to develop slowly and you will be in full control of when it stops. Your Heart Rate and Blood Pressure will be monitored throughout the procedure to monitor any changes.

You are free to withdraw from the study at any stage and you do not have to give a reason. All data will be anonymised as much as possible. Your name will be replaced with a participant number, and it will not be possible for you to be identified in any reporting of the data gathered. The results may be published in a peer-reviewed journal or presented at a conference.

If you would like to contact an independent person, who knows about this project but is not involved in it, you are welcome to contact Mr Chee-Wee Tan (Independent Advisor). Their contact details are given below.

If you have read and understood this information sheet, any questions you had have been answered, and you would like to be a participant in the study, please now see the exclusion criteria questionnaire.

	Contact Details of the Researcher	Contact Details of the Independent Advisor
<b>Name:</b>	Chris Seenan	Chee-Wee Tan
<b>Address:</b>	PhD Student, Physiotherapy, School of Health Sciences Queen Margaret University Queen Margaret University Drive Musselburgh East Lothian EH21 6UU	Physiotherapy Staff, School of Health Sciences Queen Margaret University Queen Margaret University Drive Musselburgh East Lothian EH21 6UU
<b>Email</b>	<a href="mailto:cseenan@gmu.ac.uk">cseenan@gmu.ac.uk</a>	<a href="mailto:ctan@gmu.ac.uk">ctan@gmu.ac.uk</a>
<b>Telephone:</b>	0131 474 0000	0131 474 0000



Queen Margaret University  
EDINBURGH

### EXCLUSION CRITERIA QUESTIONNAIRE

#### **Laboratory and clinical investigation into lower limb ischaemic pain, and the effect of Transcutaneous Electrical Nerve Stimulation (TENS) on measures of pain and exercise performance**

It is important that you do not have any contraindications to the techniques that will be used within this study.

Do you have any of the following?

- ☐ Any previous history of Deep Vein Thrombosis (DVT) or clotting abnormalities
- ☐ Diabetes
- ☐ Vascular pathologies of the upper or lower limb (e.g. Raynauds Disease, peripheral vascular abnormalities)
- ☐ Other circulatory problems
- ☐ A history of altered blood pressure (e.g. hypertension or hypotension)
- ☐ Other cardiovascular conditions
- ☐ Current pain anywhere in your body
- ☐ Previous chronic pain (constant pain lasting more than 2 weeks)
- ☐ Current or previous sensation abnormalities in your upper or lower limbs
- ☐ Recent trauma to your lower limbs
- ☐ Previous serious trauma to your lower limbs
- ☐ Peripheral neuropathies, e.g. Sensation abnormalities in your legs or feet
- ☐ Epilepsy
- ☐ Cardiac pacemaker
- ☐ Medical diagnosis including cardiovascular disorder or self-reported psychiatric illness
- ☐ Pregnant or trying to become pregnant
- ☐ Currently taking pain medication, regular aspirin, statins or the contraceptive pill
- ☐ Susceptible to skin reactions or have broken / damaged skin on your thigh

Thank you for volunteering but if you answered yes to any of these questions unfortunately you are unable to participate in the study.

If you are unsure about any one of these conditions or feel you have one of these conditions but not yet diagnosed please inform the researcher and seek medical assistance before continuing with the study.

Information regarding seeking medical advice or assistance is available from the researcher. In addition, the contact details for NHS 24 where you can find information about registering with a gp or seek general medical advice are as follows:

Tel: 08454 24 24 24    Website: [www.nhs24.com](http://www.nhs24.com)

---

(To be completed by the researcher)

Subject Number: \_\_\_\_\_  
Age (18+) \_\_\_\_\_  
Height \_\_\_\_\_  
Weight \_\_\_\_\_  
Blood Pressure: \_\_\_\_\_ / \_\_\_\_\_  
Heart Rate: \_\_\_\_\_  
Thigh Circumference: \_\_\_\_\_  
Registered with GP? \_\_\_\_\_ YES/NO  
Happy and able to seek medical advice if needed? YES/NO

(If **NO** to either, ensure registration and provide information if needed prior to taking part in the study)



Queen Margaret University  
EDINBURGH

## CONSENT FORM

### **Laboratory and clinical investigation into lower limb ischaemic pain, and the effect of Transcutaneous Electrical Nerve Stimulation (TENS) on measures of pain and exercise performance**

I, \_\_\_\_\_ agree to take part in the above study. The purpose of the study has been explained to me and I understand that I may experience a level of pain during testing.

I have read and understand the information sheet provided and have completed the Exclusion Criteria Questionnaire. I am confident that none of the exclusion criteria applies to me and if I want to seek medical advice at any point, I am willing and able to do so in confidence.

I understand that I am under no obligation to take part in this study.

If I participate in this study, I understand that if at any stage I decide I no longer wish to take part, I can withdraw at any time giving no reason.

If I have any further questions regarding this study, I understand that I can contact Mr Chee-Wee Tan (Independent Advisor).

I agree to participate in this study.

Signature of participant: \_\_\_\_\_

Signature of researcher: \_\_\_\_\_

Date: \_\_\_\_\_

	Contact Details of the Researcher	Contact Details of the Independent Advisor
<b>Name:</b>	Chris Seenan	Chee-Wee Tan
<b>Address:</b>	PhD Student, Physiotherapy, School of Health Sciences Queen Margaret University Queen Margaret University Drive Musselburgh East Lothian EH21 6UU	Physiotherapy Staff, School of Health Sciences Queen Margaret University Queen Margaret University Drive Musselburgh East Lothian EH21 6UU
<b>Email</b>	<a href="mailto:cseenan@gmu.ac.uk">cseenan@gmu.ac.uk</a>	<a href="mailto:ctan@gmu.ac.uk">ctan@gmu.ac.uk</a>
<b>Telephone:</b>	0131 474 0000	0131 474 0000



#### 14.7: APPENDIX 7: RANDOMISATION PROCEDURE FOR TREADMILL STUDY

---

Block Randomisation:

Participant No.	Group
1	1
2	2
3	1
4	2
5	1
6	2
7	1
8	2
9	1
10	2
11	1
12	1
13	2
14	1
15	2
16	1
17	2
18	1
19	1
20	2
21	1
22	2
23	1
24	2
25	1
26	2
27	1
28	1
29	2
30	1
31	2
32	1
33	2
34	1
35	2
36	1
37	2
38	2
39	2
40	2



Queen Margaret University  
EDINBURGH

## **Participant Information Sheet**

**A pilot study into patients' experiences of pain and mobilising with Peripheral Arterial Disease (PAD) and the effects of Transcutaneous Electrical Nerve Stimulation (TENS) on pain and treadmill walking**

*This study has been reviewed by a NHS Research Ethics Committee, which has responsibility for scrutinising proposals for medical research on humans. In this case, the reviewing Committee was the Tayside Research Ethics Committee who have raised no objections from the point of view of medical ethics.'*

My name is Chris Seenan and I am a PhD Student at Queen Margaret University, Edinburgh. I am required to undertake a project as part of my course and invite you to take part in the following study. However, before you decide to do so, I need you to understand firstly why I am doing it, and secondly what it would involve if you agreed. I am therefore providing you with the following information. Please read it carefully and be sure to ask any questions you might have and, if you want, discuss it with others including your friends and family. I will do my best to explain the project to you and provide you with any further information you may ask for now or later.

We would like to invite you to participate in a research project. We believe it to be of potential importance. Before you decide whether or not to take part it is important for you to understand why the research is being done and what it will involve if you decide to take part. Please take time to read the following information carefully and be sure to ask any questions that you have and if you want, discuss it with family, friends or your GP. We will do our best to explain and to provide any further information you may ask now or later. You do not have to make an immediate decision.

**What is the purpose of the study?**

You have been invited to take part in this project as you have been diagnosed with Peripheral Arterial Disease (PAD). Your consultant has recommended that you might be suitable to participate as you experience pain in your leg(s) while walking.

One of the main aims of this study is to examine the pain you experience which is called 'Intermittent Claudication' (IC). We aim to record a detailed account of this pain from a patient's perspective. We would also like to examine the effects of a commonly used, non-pharmaceutical treatment called Transcutaneous Electrical Nerve Stimulation (TENS). TENS is widely used but has yet to be tested for IC pain. We will measure your walking distance on the treadmill and test different dosages of TENS. Your treatment dosage will be randomly selected to avoid biasing the result.

The findings of the project will hopefully improve the understanding of the pain you experience and its effect on walking performance. It may also provide an indication of the usefulness of TENS.

**Why have I been chosen?**

Your doctor has suggested that you may be suitable to participate in this study if you wish to do so. Your name has been suggested because you have PAD and experience pain in your leg when walking. The pain is called Intermittent Claudication (IC). We are planning to study other people with the same medical condition as you.

**What will I have to do if I take part?**

No new drugs will be given as part of this study.

If you agree to take part in the study, you will be asked to attend on two occasions. When you attend for the first visit, you will be asked to complete five, one page, tick-box questionnaires; rest for 15 minutes, walk on a treadmill and complete another questionnaire. The second visit will be shorter as you will be asked to walk on the treadmill and complete one questionnaire.

During each treadmill test you will be asked to report when you feel the claudication pain. We will ask you to walk on until you reach the point where you cannot walk any further due to the pain in your leg(s). Despite the severity of this pain, it is transient and will resolve with rest. While you rest and the pain reduces, we will ask you to describe in detail, the pain you experienced using a simple questionnaire, administered by the researcher. During the treadmill walking the TENS device will be attached to one of your legs and set to a specific dosage.

At the end of each testing session, you will be asked to complete a short questionnaire. This will include questions about your experience during the testing procedure and your opinion of TENS as a treatment option for your condition.

Apart from this, you do not have to do anything different from your normal lifestyle and the trial does not affect your current treatment. You will also be reimbursed for any travel expenses you incur.

**Where will the research be conducted?**

The research will be conducted in The Vascular and Inflammatory Diseases Research Unit, in the Institute of Cardiovascular Research, Ninewells Hospital and Medical School, Dundee.

What are the benefits of taking part in this study?

There are no immediate benefits to you as an individual.

**What are the risks of the test involved?**

There are no foreseeable risks in participating in this research. You will experience pain during the treadmill walking. When you develop pain, it is expected to develop slowly and once you stop, the pain will resolve. You will be connected to a heart rate monitor throughout the test.

**What are my rights?**

We will inform you of the results of the study and which treatment you received. With your permission, we will contact your GP to let him/her know about your participation in the study. Participation in this study is entirely voluntary and you are free to refuse to take part or to withdraw from the study at any time without having to give a reason and without this affecting your future medical care or your relationship with medical staff looking after you.

**Will the research influence the treatment I receive?**

The research does not alter the treatment you receive. Your consultant and GP will start and stop treatments as determined by your clinical condition.

**Should I let my health insurance company know?**

Some insurance companies consider that participation in medical research such as this is a "material fact" which should be mentioned in any proposal for health-related insurance, or which could influence their judgment in consideration of claims made under existing insurance policies. You should check that participation in this research does not affect any policy you might be thinking about taking.

**Will my taking part in the study be kept confidential?**

The information collected about you in this study will be anonymised i.e. linked to a special code that is stored separately on a password-protected computer file. All information that is collected about you during the course of the research will be kept strictly confidential.

No one outside the research team will have any access to any identifying information. All identifiable information will be kept securely and will be retained for a period of 3 months after the study ends.

**Who is organizing and coordinating the study?**

This study is being coordinated by Queen Margaret University, Edinburgh and The Institute of Cardiovascular Research, University of Dundee.

The Tayside Research Ethics Committee B, that has responsibility for scrutinizing proposals for medical research on humans in Tayside, has examined the proposal and has raised no objections from the point of view of medical ethics. It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors from NHS Tayside.

If you would like any further information regarding this study you can contact the researcher or the medical staff involved in the study (Contact details below).

Even after you agree to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

Thank you for taking the time to read this Information Sheet and considering taking part in the study. You will be given a copy of this information sheet and a signed consent form for your records.

Contact Details of the Researchers		
<b>Name:</b>	Chris Seenan	Steve McSwiggan
<b>Address:</b>	PhD Research Student, Physiotherapy, School of Health Sciences Queen Margaret University Edinburgh EH21 6UU	Senior Research Nurse, Study Coordinator, Vascular & Inflammatory Diseases Research Unit The Institute of Cardiovascular Research Ninewells Hospital & Medical School, Dundee DD1 9SY
<b>Email</b>	<a href="mailto:cseenan@qmu.ac.uk">cseenan@qmu.ac.uk</a>	<a href="mailto:s.j.mcswiggan@dundee.ac.uk">s.j.mcswiggan@dundee.ac.uk</a>
<b>Telephone:</b>	0131 474 0000 Ext 4795	01382 660111 Ext 34147, Bleep 4258

Contact Details of the Independent Advisor	
<b>Name:</b>	Dr John Dick
<b>Address:</b>	Consultant Vascular Physician Wards 3 & 4 Ninewells Hospital and Medical School Dundee DD1 9SY
<b>Email</b>	
<b>Telephone:</b>	01382 660111



**Participant Reply Slip**

***A pilot study into patients' experiences of pain and mobilising with Peripheral Arterial Disease (PAD) and the effects of Transcutaneous Electrical Nerve Stimulation (TENS) on pain and treadmill walking***

**Name:**

**Address:**

**Tel:**

**Email:**

**Availability to meet at Ninewells:**

	<i>Mon</i>	<i>Tues</i>	<i>Wed</i>	<i>Thurs</i>	<i>Fri</i>	<i>Sat</i>	<i>Sun</i>
<i>am</i>							
<i>pm</i>							

**Comments:**

.....  
.....



Queen Margaret University  
EDINBURGH

## **Participant Consent Form**

### **A pilot study into patients' experiences of pain and mobilising with Peripheral Arterial Disease (PAD) and the effects of Transcutaneous Electrical Nerve Stimulation (TENS) on pain and treadmill walking**

Name of Researcher: Christopher Seenan

**Please initial box**

1. I confirm that I have read and understand the information sheet dated April 2009 (Version 2) for the above study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from Queen Margaret University, from regulatory authorities or from NHS Tayside, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
4. I agree to my GP being informed of my participation in the study
5. I agree to take part in the above study.

\_\_\_\_\_  
Name of Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of Person taking consent  
(If different from researcher)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Researcher

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature



### **Instructions for completing the questionnaires:**

Please could you read carefully and answer the following four, short questionnaires (provided on separate sheets):

1. Walking Impairment Questionnaire (WIQ)
2. Pain Self Efficacy Questionnaire (PSEQ)
3. Pain Catastrophising Scale (PCS)
4. Tampa Scale of Kinesiophobia (TSK)

For the first three questionnaires, there are instructions on the top to explain what you need to do. If you are unsure about any of them or would like some clarification, please ask the researcher.

**When you reach the fourth questionnaire (the Tampa Scale of Kinesiophobia) let the researcher know and they will explain it to you.**

If you have any questions or are unsure about any of the questionnaires, at any point, please don't hesitate to ask the researcher.

## Walking Impairment Questionnaire

1. Please place a V in the box that best describes how much difficulty you have had due to pain, aches or cramps during the last week. The response options range from 'No Difficulty' to 'Great Difficulty'.

<i><b>During the last week, how much difficulty have you had walking due to:</b></i>	<b>No Difficulty</b>	<b>Slight Difficulty</b>	<b>Some Difficulty</b>	<b>Much Difficulty</b>	<b>Great Difficulty</b>
a. Pain, aching, or cramps in your calves?					
b. Pain, aching, or cramps in your buttocks?					

For the following questions, the response options range from 'No Difficulty' to 'Unable to Do'. If you **cannot physically perform** a specified activity, for example walk 600 feet (100 metres) without stopping to rest because of symptoms such as leg pain or discomfort, please place a V in the box labelled 'Unable to Do'.

However, if you **do not perform** an activity for reasons unrelated to your circulation problems, such as climbing a flight of stairs because your home is on one level or you flat has a lift, please place a V in the box 'Don't Do For Other Reasons'.

2. Please place a *✓* in the box that best describes how hard it was for you to walk on level ground without stopping to rest for each of the following distances during the last week:

<i>During the last week, how difficult was it for you to:</i>	<b>No Difficulty</b>	<b>Slight Difficulty</b>	<b>Some Difficulty</b>	<b>Much Difficulty</b>	<b>Unable to Do</b>	<b>Didn't Do For Other Reasons</b>
a. <b>Walk indoors</b> , such as around your home?						
b. <b>Walk 50 feet</b> (~15 metres)?						
c. <b>Walk 150 feet</b> (~45 metres)?						
d. <b>Walk 300 feet</b> (~90 metres)?						
e. <b>Walk 600 feet</b> (~180 metres)?						
f. <b>Walk 900 feet</b> (~270 metres)?						
g. <b>Walk 1500 feet</b> (~450 metres)?						

3. Please place a ✓ in the box that best describes how hard it was for you to walk 300 feet (roughly 90 metres) on level ground at each of these speeds without stopping to rest during the last week.

<i>During the last week, how difficult was it for you to:</i>	<b>No Difficulty</b>	<b>Slight Difficulty</b>	<b>Some Difficulty</b>	<b>Much Difficulty</b>	<b>Unable to Do</b>	<b>Didn't Do For Other Reasons</b>
a. Walk 300 feet slowly?						
b. Walk 300 feet at an average speed?						
c. Walk 300 feet quickly?						
d. Run or jog 300 feet?						

4. Please place a ✓ in the box that best describes how hard it was for you to climb stairs without stopping to rest during the last week. Please note 1 flight of stairs is roughly equal to 14 steps.

<i>During the last week, how difficult was it for you to:</i>	<b>No Difficulty</b>	<b>Slight Difficulty</b>	<b>Some Difficulty</b>	<b>Much Difficulty</b>	<b>Unable to Do</b>	<b>Didn't Do For Other Reasons</b>
a. Climb 1 flight of stairs?						
b. Climb 2 flights of stairs?						
c. Climb 3 flights of stairs?						

## **PAIN SELF EFFICACY QUESTIONNAIRE**

- **Please answer the following questions in relation to how you feel right now**

**PAIN SELF EFFICACY QUESTIONNAIRE (PSEQ)**  
M.K.Nicholas (1989)

NAME: \_\_\_\_\_ DATE: \_\_\_\_\_

Please rate how **confident** you are that you can do the following things at present, **despite the pain**. To indicate your answer circle **one** of the numbers on the scale under each item, where 0 = not at all confident and 6 = completely confident.

For example:

0	1	2	3	4	5	6
Not at all Confident						Completely confident

Remember, this questionnaire is **not** asking whether or not you have been doing these things, but rather **how confident** you are that you can do them at present, despite the pain.

---

1. I can enjoy things, despite the pain.

0	1	2	3	4	5	6
Not at all Confident						Completely confident

2. I can do most of the household chores (e.g. tidying-up, washing dishes, etc.), despite the pain.

0	1	2	3	4	5	6
Not at all Confident						Completely confident

3. I can socialise with my friends or family members as often as I used to do, despite the pain.

0	1	2	3	4	5	6
Not at all Confident						Completely confident

4. I can cope with my pain in most situations.

0	1	2	3	4	5	6
Not at all Confident						Completely confident

Turn over

5. I can do some form of work, despite the pain. ("work" includes housework, paid and unpaid work).

0 1 2 3 4 5 6  
Not at all Completely  
Confident confident

6. I can still do many of the things I enjoy doing, such as hobbies or leisure activity, despite pain.

0 1 2 3 4 5 6  
Not at all Completely  
Confident confident

7. I can cope with my pain without medication.

0 1 2 3 4 5 6  
Not at all Completely  
Confident confident

8. I can still accomplish most of my goals in life, despite the pain.

0 1 2 3 4 5 6  
Not at all Completely  
Confident confident

9. I can live a normal lifestyle, despite the pain.

0 1 2 3 4 5 6  
Not at all Completely  
Confident confident

10. I can gradually become more active, despite the pain.

0 1 2 3 4 5 6  
Not at all Completely  
Confident confident

Source: Nicholas M.K. Self-efficacy and chronic pain. Paper presented at the annual conference of the British Psychological Society. St. Andrews, 1989.  
Reprinted with permission from the author

## **PAIN CATASTROPHIZING SCALE**

- Please answer the following questions in relation to how you feel right now



## Pain Catastrophizing Scale

Sullivan MJL, Bishop S, Pivik J. (1995)

---

Name:	Age:	Gender:	Date:
_____	_____	<input type="checkbox"/> Male <input type="checkbox"/> Female	_____

---

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

**Instructions:**

*We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.*

RATING	0	1	2	3	4
MEANING	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

*When I'm in pain ...*

Number	Statement	Rating
1	I worry all the time about whether the pain will end.	
2	I feel I can't go on.	
3	It's terrible and I think it's never going to get any better	
4	It's awful and I feel that it overwhelms me.	
5	I feel I can't stand it anymore	
6	I become afraid that the pain will get worse.	
7	I keep thinking of other painful events	
8	I anxiously want the pain to go away	
9	I can't seem to keep it out of my mind	
10	I keep thinking about how much it hurts.	
11	I keep thinking about how badly I want the pain to stop	
12	There's nothing I can do to reduce the intensity of the pain	
13	I wonder whether something serious may happen.	

Copyright 1995 Michael J.L. Sullivan. Reproduced with permission.

Source: Sullivan MJL, Bishop S, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess*, 1995, 7: 524-532

# Tampa Scale for Kinesiophobia (Miller, Kori and Todd 1991)

1 = strongly disagree

2 = disagree

3 = agree

4 = strongly agree

1. I'm afraid that I might injury myself if I exercise	1	2	3	4
2. If I were to try to overcome it, my pain would increase	1	2	3	4
3. My body is telling me I have something dangerously wrong	1	2	3	4
4. My pain would probably be relieved if I were to exercise	1	2	3	4
5. People aren't taking my medical condition seriously enough	1	2	3	4
6. My accident has put my body at risk for the rest of my life	1	2	3	4
7. Pain always means I have injured my body	1	2	3	4
8. Just because something aggravates my pain does not mean it is dangerous	1	2	3	4
9. I am afraid that I might injure myself accidentally	1	2	3	4
10. Simply being careful that I do not make any unnecessary movements is the safest thing I can do to prevent my pain from worsening	1	2	3	4
11. I wouldn't have this much pain if there weren't something potentially dangerous going on in my body	1	2	3	4
12. Although my condition is painful, I would be better off if I were physically active	1	2	3	4
13. Pain lets me know when to stop exercising so that I don't injure myself	1	2	3	4
14. It's really not safe for a person with a condition like mine to be physically active	1	2	3	4
15. I can't do all the things normal people do because it's too easy for me to get injured	1	2	3	4
16. Even though something is causing me a lot of pain, I don't think it's actually dangerous	1	2	3	4
17. No one should have to exercise when he/she is in pain	1	2	3	4

Reprinted from:

*Pain, Fear of movement/(re) injury in chronic low back pain and its relation to behavioral performance.* 62, Vlaeyen, J., Kole-Snijders A., Boeren R., van Eek H., 371.

Copyright (1995) with permission from International Association for the Study of Pain.

NINEWELLS HOSPITAL AND MEDICAL SCHOOL  
DUNDEE DD1 9SY  
SCOTLAND

## STANDARD OPERATING PROCEDURE

**TITLE:** How to measure Initial Claudication Distance (ICD) and Absolute Claudication Distance (ACD) in patients with Peripheral Arterial Disease (PAD)

COMPILED BY	Signed	_____
	Date	_____
APPROVED BY	Signed	_____
	Date	_____

## **1. PURPOSE**

The purpose of this Standard Operating Procedure is to describe the procedure used for the measurements of Initial Claudication Distance (ICD) and Absolute Claudication Distance (ACD) on exercise treadmill.

## **2. SCOPE**

This SOP is intended for use by personnel who have been trained in this procedure.

## **3. RESPONSIBILITY**

All Members of Clinical staff performing this procedure will be responsible for complying with the details of this procedure

## **4. PROCEDURE**

### **4.1 Treadmill Test Definitions**

**Absolute Claudication Distance (ACD)** is defined as the maximum distance in metres and centimetres walked by a patient on a treadmill under standardized conditions. The patient should continue the test until walking can no longer be tolerated because of claudication symptoms. It is critical that the patient **not** stop walking when they normally would do so. The patient should be asked to continue to walk until they feel they must stop due to claudication symptoms.

**Initial Claudication Distance (ICD)** is defined as the distance in metres and centimetres walked by a patient on a treadmill under standardized conditions before the onset of claudication symptoms, regardless of whether this is manifested or characterized as muscle pain, ache, cramp, numbness or fatigue. This does not include joint pain or other pain not associated with claudication.

### **4.2 Treadmill Set Up**

**The treadmill must be programmed with the attached Gardner protocol** (see Table 1)

The treadmill's function **must** be assessed routinely by the designated staff.

The treadmill room should be free of distractions that might interfere with the treadmill test. Ideally, there should be a bed next to the treadmill to accommodate pre-exercise and post-exercise ABI testing. The treadmill should be situated such that the staff are able to assist the patient if they have difficulty while on the treadmill.

### **Treadmill Familiarization**

A short familiarization session on the treadmill **must** precede the official treadmill test in screening phases of studies. The treadmill familiarization should begin at a slow treadmill speed of 1.0 mph and 0% grade. Familiarization should also include walking bouts at 1.5 mph and 2.0 mph. Each bout of walking should only last between 10 to 15 seconds, but may be repeated as necessary. The treadmill belt should be stopped between each bout of walking so the patient can get comfortable transitioning from straddling the belt to walking on the belt.

1. Prior to the patient performing the treadmill test, they should be advised to immediately notify the staff performing the treadmill test if they experience any physical difficulty such as chest pain / discomfort, shortness of breath (SOB), or lightheadedness. If this occurs, the treadmill should be stopped immediately and appropriate medical intervention should be administered.
2. Have the patient straddle the treadmill belt and step on it once it is fully up to speed at 1.0, 1.5 and 2.0 mph for a minimum of 3 separate bouts of walking. A maximum of 10secs walking on the treadmill at each speed. Additional bouts of walking may be repeated as necessary.
3. During familiarization the patient should be instructed to walk on a treadmill in as normal a manner as possible. Make sure they are using a normal stride and not doing a shortened stutter step or shuffle step. They should be instructed to walk with their back straight and looking forward instead of looking down at the belt as this may make them dizzy.
4. Also, make sure the patient walks on the treadmill with their hands resting lightly on the rail, for balance only. Discourage the patient from using the rail for support.
5. This treadmill familiarization should be repeated as often as necessary during the course of the trial.

#### **Before the Treadmill Test**

The treadmill controller timer should be used to measure ICD and ACD. In some cases a stopwatch or other suitable timing device may be used. Time should be recorded in \_min \_sec format.

Continuous ECG testing is strongly recommended during treadmill testing.

It is strongly recommended that the treadmill test be performed at a consistent time of day.

1. The patient must rest for at least 10 minutes prior to the test.
2. Patients should refrain from consuming any alcoholic beverage prior to the test (i.e., on the day of the test). Smoking is not permitted within 2 hours of the test.
3. The room should be maintained at a comfortable temperature.
4. The patient must wear a pair of comfortable shoes.
5. The patient must not wear a watch and must be positioned where he/she cannot see a clock or timer during the test.
6. Carefully explain ACD to the patient prior to the treadmill test (i.e. "We want you to walk as far as you possibly can").
7. Explain the Claudication Symptom Rating Scale (see Appendix 1) to the patient prior to treadmill testing. Ensure this scale is posted directly in front of the treadmill where the patient can easily refer to it.
8. Stress to the patient that they must let the staff know the moment they begin to experience claudication symptoms during the treadmill test. This corresponds to "2-Onset" of the Claudication Symptom Rating Scale.
9. Assess what words the patient uses to describe their claudication symptoms. Be certain to use the same words when questioning the subject about their claudication symptoms during the treadmill.

10. Instruct the subject to let you know if they experience SOB, chest pain or dizziness during the treadmill.
11. At the screening visit, patients who are forced to discontinue walking for reasons other than ischemic leg pain (e.g., angina pectoris, dyspnoea, dizziness, etc.) must be excluded from the study.

### Starting the Treadmill Test

1. When starting the actual treadmill test, ensure the treadmill belt is moving at 2.0 mph before the patient steps on and before starting the Gardner protocol.
2. Be sure to start the Gardner protocol and timing for both the ACD and ICD when the subject's second heel makes contact with the treadmill belt.
3. Ask the patient to rate their claudication symptoms using the Claudication Symptom Rating Scale frequently throughout the treadmill testing. Remind them to let you know the moment their symptoms start which equals the number 2 – onset on the scale.
4. Give the same feedback/encouragement to each patient.
5. Document the ICD when the patient first begins to experience claudication symptoms.
6. Ensure that the patient is walking with a comfortable gait.
7. Ensure that the patient is using the bar on the treadmill for balance only.

### Ending the Treadmill Test

1. Remember that number 5 – Severe on the Claudication Rating Scale does not mean that the patient should stop walking. Many patients can continue walking even though their symptoms are severe.
2. Encourage the patient to continue walking until they can no longer tolerate walking due to claudication symptoms.
3. When the patient states that they must stop and ACD is achieved, stop the treadmill belt and the timer at the same time.
4. Transfer the patient to a chair or exam table to rest after the treadmill testing is completed.
5. Verify the reason that the patient stopped the treadmill test and document both the reason stopped and the ACD.
6. If the patient experiences SOB, chest pain, dizziness, significant ECG changes or any other significant sign or symptom that makes the site staff concerned for the patient's safety, **STOP** the treadmill test **IMMEDIATELY** and **take appropriate medical intervention.**

## Gardner Treadmill Protocol for Peripheral Arterial Disease Patients with Intermittent Claudication

**Table 1**

Stage	Speed (mph)	Elevation (% grade)	Duration (min)
-------	----------------	------------------------	-------------------

Rest/Recovery*	2.0	0	-
1	2.0	0	2 minutes
2	2.0	2	2 minutes
3	2.0	4	2 minutes
4	2.0	6	2 minutes
5	2.0	8	2 minutes
6	2.0	10	2 minutes
7	2.0	12	2 minutes
8	2.0	14	2 minutes
9	2.0	16	2 minutes
10	2.0	18	2 minutes
11	2.0	18	At least 20 minutes

- \* On some treadmills this stage may be called Sitting, Supine and / or Standing. Other treadmills may not have this stage. The purpose of this stage is to get the belt up to 2 mph prior to the patient stepping on the belt. The patient should not straddle the belt for longer than necessary.

## 5. HISTORY OF REVISION

This SOP supersedes all previous versions of this SOP.

1- None

2- Onset

3- Mild

4- Moderate

5- Severe





Queen Margaret University

EDINBURGH

Chris Seenan  
School of Health  
Glasgow Caledonian University  
Cowcaddens Road  
Glasgow  
G4 0BA  
0141 331 8151  
chris.seenan@gcu.ac.uk

**A pilot study into patients' experiences of pain and mobilising with Peripheral Arterial Disease (PAD) and the effects of Transcutaneous Electrical Nerve Stimulation (TENS) on pain and treadmill walking**

Dear ,

Thank you for participating in the above study. Your participation was extremely valuable and informative.

I am contacting you to make you aware of the results from the study for your information. We found that the TENS device under investigation increased the distance walked on a treadmill, compared to non-functioning TENS. The device however, does not appear to have any effect on the pain experienced during walking.

These are very interesting results. Despite this, and as I mentioned before, this was merely a pilot study and further investigation is required to confirm the findings.

Therefore, we are now looking to progress the research and the next step is to investigate the experience of using a TENS device at home for patients with your condition.

To do this, we are planning to conduct a study where we provide TENS devices and training to a number of people with your condition and ask them to use it in their daily life for one month. At the end of this month we will ask these people to attend a focus group where they will discuss their experiences with one another and a researcher.

If you are interested in participating in this study, please read the attached information sheet thoroughly, discuss it with your family and friends and use the reply slip and pre-paid envelope provided. If, for whatever reason, you are not interested, please disregard all of this and we thank you again for your contribution to the study.

Yours sincerely,

Chris Seenan  
PhD research student



Queen Margaret University  
EDINBURGH

## **Participant Information Sheet**

### **A pilot investigation into patients' experiences of using Transcutaneous Electrical Nerve Stimulation (TENS) for daily life with Peripheral Arterial Disease (PAD) and Intermittent Claudication (IC)**

We would like to invite you to participate in a research project. We believe it to be of potential importance. Before you decide whether or not to take part it is important for you to understand why the research is being done and what it will involve if you decide to take part. Please take time to read the following information carefully and be sure to ask any questions that you have and if you want, discuss it with family, friends or your GP. We will do our best to explain and to provide any further information you may ask now or later. You do not have to make an immediate decision.

#### **What is the purpose of the study?**

You have been invited to take part in this project as you have been diagnosed with Peripheral Arterial Disease (PAD). Your consultant has recommended that you might be suitable to participate as you experience pain in your leg(s) while walking.

One of the main aims of this study is to examine the pain you experience which is called 'Intermittent Claudication' (IC). We would like to investigate the experience of patients with PAD and IC using a non-pharmaceutical treatment called Transcutaneous Electrical Nerve Stimulation (TENS) at home for normal daily activities.

The findings of the project will hopefully improve the understanding of the pain you experience and its effect on walking performance. It may also provide an indication of the usefulness of TENS for your condition.

#### **Why have I been chosen?**

Your consultant has suggested that you may be suitable to participate in this study if you wish to do so. Your name has been suggested because you have PAD and experience pain in your leg when walking. The pain is called Intermittent Claudication (IC). We are planning to study other people with the same medical condition as you.

**What will I have to do if I take part?**

*No new drugs will be given as part of this study.*

If you agree to take part in the study, the researcher will arrange a time for you to visit Ninewells Hospital to provide you with a TENS device and training. During this visit you will have an opportunity to ask any questions and then you will be asked to take the TENS machine home and use it daily. You will be given training in how to use the TENS device correctly and safely and asked to complete two, short, tick-box questionnaires. At the end of one month you will be asked to attend Ninewells Hospital in Dundee to take part in a focus group and complete three, short, tick-box questionnaires.

Apart from this, you do not have to do anything different from your normal lifestyle and the trial does not affect your current treatment. You will also be reimbursed for any travel expenses you incur.

**Where will the research be conducted?**

The research will be conducted in The Vascular and Inflammatory Diseases Research Unit, in the Institute of Cardiovascular Research, Ninewells Hospital and Medical School, Dundee.

**What are the benefits of taking part in this study?**

If the TENS machine is effective, you may experience a reduction in pain when using the device.

**What are the risks involved?**

There is a risk of allergy and skin reaction to the pads used with the TENS device. If this occurs you will be advised to stop using the device immediately. Full safety training and instructions for using the TENS device will be provided.

**What are my rights?**

We will inform you of the results of the study. With your permission, we will contact your GP to let him/her know about your participation in the study. Participation in this study is entirely voluntary and you are free to refuse to take part or to withdraw from the study at any time without having to give a reason and without this affecting your future medical care or your relationship with medical staff looking after you. If you do withdraw from the study after providing written consent, you will not be contacted from that point forward however, any data gathered up to that point will still be used in the study.

**Will the research influence the treatment I receive?**

The research does not alter the treatment you receive. Your consultant and GP will start and stop treatments as determined by your clinical condition.

**Should I let my health insurance company know?**

Some insurance companies consider that participation in medical research such as this is a "material fact" which should be mentioned in any proposal for health-related insurance, or which could influence their judgment in consideration of claims made under existing

insurance policies. You should check that participation in this research does not affect any policy you might be thinking about taking.

**Will my taking part in the study be kept confidential?**

The information collected about you in this study will be anonymised i.e. linked to a special code that is stored separately on a password-protected computer file. All information that is collected about you during the course of the research will be kept strictly confidential.

No one outside the research team will have any access to any identifying information. All identifiable information will be kept securely and will be retained for a period of 3 months after the study ends.

**Who is organizing and coordinating the study?**

This study is being coordinated by Queen Margaret University, Edinburgh and The Institute of Cardiovascular Research, University of Dundee.

The Tayside Committee on medical Research Ethics B, which has responsibility for scrutinizing all proposals for medical research on humans in Fife, Forth Valley and Tayside, has examined the proposal and has raised no objections from the point of view of medical ethics. It is a requirement that your records in this research be made available for scrutiny by monitors from Queen Margaret University and NHS Tayside whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

If you would like any further information regarding this study you can contact the researcher or the medical staff involved in the study (contact details below).

Even after you agree to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

Thank you for taking the time to read this Information Sheet and considering taking part in the study.

**If you wish to take part in the study, please complete the attached reply slip and post it to us in the pre-paid envelope provided (you do not need to attach a stamp) or, if you prefer, please email either of the researchers to indicate your interest in taking part and we will get back to you: [cseenan@qmu.ac.uk](mailto:cseenan@qmu.ac.uk) or [s.j.mcswiggan@dundee.ac.uk](mailto:s.j.mcswiggan@dundee.ac.uk) (This information sheet is for you to keep)**

Contact Details of the Researchers		
<b>Name:</b>	Chris Seenan	Steve McSwiggan
<b>Address:</b>	Lecturer in Physiotherapy School of Health Glasgow Caledonian University Cowcaddens Road Glasgow G4 0BA	Senior Research Nurse, Study Coordinator, Vascular & Inflammatory Diseases Research Unit The Institute of Cardiovascular Research Ninewells Hospital & Medical School, Dundee DD1 9SY
<b>Email</b>	<a href="mailto:chris.seenan@gcu.ac.uk">chris.seenan@gcu.ac.uk</a>	<a href="mailto:s.j.mcswiggan@dundee.ac.uk">s.j.mcswiggan@dundee.ac.uk</a>
<b>Telephone:</b>	0141 331 8151 07515 645 895	01382 660111 Ext 34147, Bleep 4258

Contact Details of the Independent Advisor	
<b>Name:</b>	Dr John Dick
<b>Address:</b>	Consultant Vascular Physician Wards 3 & 4 Ninewells Hospital and Medical School Dundee DD1 9SY
<b>Telephone:</b>	01382 660111



Queen Margaret University  
EDINBURGH

**Participant Consent Form**

**A pilot investigation into patients' experiences of using Transcutaneous Electrical Nerve Stimulation (TENS) for daily life with Peripheral Arterial Disease (PAD) and Intermittent Claudication (IC)**

Name of Researcher: Christopher Seenan

**Please tick box**

- |   |                          |
|---|--------------------------|
| 1. I confirm that I have read and understand the information sheet dated 20110329 (Version 5) for the above study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.   | <input type="checkbox"/> |
| 2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.   | <input type="checkbox"/> |
| 3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from Queen Margaret University or from NHS Tayside, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. | <input type="checkbox"/> |
| 4. I agree to my GP being informed of my participation in the study   | <input type="checkbox"/> |
| 5. I agree that any data collected can be used in the study even if I withdraw  | <input type="checkbox"/> |
| 6. I agree to the use of audio recordings in the focus group and anonymised quotes in written work where applicable   | <input type="checkbox"/> |
| 7. I understand that the focus groups are private and confidentiality must be adhered to regarding anything discussed   | <input type="checkbox"/> |
| 8. I agree to take part in the above study  | <input type="checkbox"/> |

_____ Name of Participant	_____ Date	_____ Signature
_____ Name of Person taking consent (If different from researcher)	_____ Date	_____ Signature
_____ Researcher	_____ Date	_____ Signature

## 14.15: APPENDIX 15: TENS DAILY USE STUDY PARTICIPANT REPLY SHEET

---



### **Participant Reply Slip**

An investigation into patients' experiences of using Transcutaneous Electrical Nerve Stimulation (TENS) for daily life with Peripheral Arterial Disease (PAD) and Intermittent Claudication (IC)

Name: \_\_\_\_\_

Address: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Tel: \_\_\_\_\_

Email: \_\_\_\_\_

Please can you indicate the general times that you might be available to meet at Ninewells Hospital to receive your TENS device and training:

	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
am							
pm							

Comments:

.....  
.....



## Instructions for Using your PhysioMed™ TENS Device

### **Preparing and switching it on.**

1. Take the TENS device, the leads and the electrodes out of the case.
2. Lift the protective cover on the TENS device and attach the leads to the output channels (holes in the top of the device, you can use either 1 or both))
3. Connect the leads to the electrodes (2 or 4)
4. Clean the skin where you will place the electrodes.
5. Remove the electrodes from their plastic cover and attach them to the skin. If they do not stick properly, clean the skin again and use new electrodes.
6. Electrodes should be placed over the site of your pain. The electrodes must not touch each other.
7. Switch on the TENS device by slowly turning the on/off dial(s) clockwise until you feel a 'click', one at a time
8. Continue to turn the on/off dial until you feel a 'tingling' sensation
9. Once you feel the 'tingling' sensation, keep turning the on/off dial until you reach a sensation that you would describe as 'strong, but comfortable'
10. Clip the TENS device to your clothes in a safe place and make sure there are no trailing wires

### **The TENS machine should be now working correctly.**

#### **During use:**

11. Keep adjusting the on/off dial so that you maintain a 'strong, but comfortable' sensation
12. Turn the device on and off using the dial as frequently as required.
  - a. When you are sitting or resting it is advised that you turn it off.
  - b. When you are walking or active on your feet, it is advised that you turn it on (see step 11).

#### **Once you have finished using the device for the day:**

13. Turn it off using the on/off dial. Ensure that you feel a 'click' to completely turn it off.
14. Once turned off, remove the electrodes from the skin and place them back on the plastic cover.
15. Remove the leads from the TENS device and return everything to the case

**“Going for a walk is not a problem for me”**

**“There is nothing that I can do to about my disease”**

**“The worst part of the disease is the pain”**

**“TENS is the perfect treatment for walking”**

**“TENS is easy to use for people with my disease”**

**“TENS is not for me”**

**“TENS reduces the pain experience of my disease”**

**Do you have any other thoughts about TENS and/or walking activity that we may not have discussed already?**



Queen Margaret University  
EDINBURGH

## **QUESTIONNAIRES**

**A pilot study into patients' experiences of pain and mobilising with  
Peripheral Arterial Disease (PAD) and the effects of Transcutaneous Electrical  
Nerve Stimulation (TENS) on pain and treadmill walking**

- **Please take your time to complete these questionnaires**
- **You can complete them all together or separately**
- **Please return them in the envelope provided**
- **If you have any questions or queries please contact the researcher (details below)**

Chris Seenan

PhD Research Student, Physiotherapy,  
School of Health Sciences  
Queen  
Edinburgh  
EH21 6UU

Margaret

University

Tel: 0131 474 0000 (Ext 4795)

Mobile: 07515 645 895

Email: [cseenan@gmu.ac.uk](mailto:cseenan@gmu.ac.uk)

## **INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE**

- Please answer the following questions in relation to the past week

## INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

### ***PART 1: JOB-RELATED PHYSICAL ACTIVITY***

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

☐ Yes

☐ No →

***Skip to PART 2: TRANSPORTATION***

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include travelling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

\_\_\_\_\_ **days per week**

☐ No vigorous job-related physical activity



***Skip to question 4***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

\_\_\_\_\_ **hours per day**  
\_\_\_\_\_ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

\_\_\_\_\_ **days per week**

☐

No moderate job-related physical activity



***Skip to question 6***

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

\_\_\_\_\_ **hours per day**

\_\_\_\_\_ **minutes per day**

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

\_\_\_\_\_ **days per week**

☐

No job-related walking



***Skip to PART 2: TRANSPORTATION***

7. How much time did you usually spend on one of those days **walking** as part of your work?

\_\_\_\_\_ **hours per day**

\_\_\_\_\_ **minutes per day**

## ***PART 2: TRANSPORTATION PHYSICAL ACTIVITY***

These questions are about how you travelled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

\_\_\_\_\_ **days per week**

☐

No travelling in a motor vehicle



***Skip to question 10***

9. How much time did you usually spend on one of those days **travelling** in a train, bus, car, tram, or other kind of motor vehicle?

\_\_\_\_\_ hours per day  
\_\_\_\_\_ minutes per day

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

\_\_\_\_\_ days per week

☐

No bicycling from place to place



***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

\_\_\_\_\_ hours per day  
\_\_\_\_\_ minutes per day

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

\_\_\_\_\_ days per week

☐

No walking from place to place



***Skip to PART 3: HOUSEWORK,  
HOUSE MAINTENANCE, AND  
CARING FOR FAMILY***

13. How much time did you usually spend on one of those days walking from place to place?

\_\_\_\_\_ hours per day  
\_\_\_\_\_ minutes per day

### **PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY**

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shovelling snow, or digging **in the garden or yard**?

\_\_\_\_\_ **days per week**

☐

No vigorous activity in garden or yard



***Skip to question 16***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

\_\_\_\_\_ **hours per day**

\_\_\_\_\_ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

\_\_\_\_\_ **days per week**

☐

No moderate activity in garden or yard



***Skip to question 18***

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

\_\_\_\_\_ **hours per day**

\_\_\_\_\_ **minutes per day**

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

\_\_\_\_\_ **days per week**

☐

No moderate activity inside home



***Skip to PART 4: RECREATION,  
SPORT AND LEISURE-TIME  
PHYSICAL ACTIVITY***



19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

\_\_\_\_\_ **hours per day**  
\_\_\_\_\_ **minutes per day**

**PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY**

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

\_\_\_\_\_ **days per week**

☐

No walking in leisure time



***Skip to question 22***

21. How much time did you usually spend on one of those days **walking** in your leisure time?

\_\_\_\_\_ **hours per day**  
\_\_\_\_\_ **minutes per day**

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

\_\_\_\_\_ **days per week**

☐

No vigorous activity in leisure time



***Skip to question 24***

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

\_\_\_\_\_ **hours per day** \_\_\_\_\_ **minutes per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

\_\_\_\_\_ **days per week**

☐

No moderate activity in leisure time



***Skip to PART 5: TIME SPENT SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?

\_\_\_\_\_ **hours per day**

\_\_\_\_\_ **minutes per day**

***PART 5: TIME SPENT SITTING***

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

\_\_\_\_\_ **hours per day**

\_\_\_\_\_ **minutes per day**

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

\_\_\_\_\_ **hours per day**

\_\_\_\_\_ **minutes per day**

## VASCUQOL QUESTIONNAIRE

- Please answer the following questions in relation to the past two weeks

## VASCUQOL QUESTIONNAIRE

The following questions are about how you have been affected by the poor circulation in your legs in the past two weeks. You will be asked about the symptoms you have had, the way that your activities have been affected, and how you have been feeling.

***For each question please read all of the answers and then check the one that applies best to you. For example:***

**19. In the last two weeks, problems caused by poor circulation in my legs have made me feel frustrated....**

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

***So if you had felt frustrated "hardly any of the time" your answer would be:***

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

***If you are not sure about how to answer a question then please give the best answer you can. There are no right or wrong answers. Please answer every question. Thank you***

1. During the past two weeks, **I have had pain in my leg (or foot) when walking....**
  - ☐ All of the time
  - ☐ Most of the time
  - ☐ Much of the time
  - ☐ Some of the time
  - ☐ A little of the time
  - ☐ Hardly any of the time
  - ☐ None of the time
2. During the past two weeks, **I have been worried that I might injure my leg....**
  - ☐ All of the time
  - ☐ Most of the time
  - ☐ Much of the time
  - ☐ Some of the time
  - ☐ A little of the time
  - ☐ Hardly any of the time
  - ☐ None of the time
3. During the past two weeks, **cold feet have given me....**
  - ☐ A very great deal of discomfort or distress
  - ☐ A great deal of discomfort or distress
  - ☐ A good deal of discomfort or distress
  - ☐ A moderate amount of discomfort or distress
  - ☐ Some discomfort or distress
  - ☐ Very little discomfort or distress
  - ☐ No discomfort or distress
4. During the past two weeks, because of the poor circulation to my legs, **my ability to exercise or to play sports has been....**
  - ☐ Totally limited, couldn't exercise at all
  - ☐ Extremely limited
  - ☐ Very limited
  - ☐ Moderately limited
  - ☐ A little limited
  - ☐ Only very slightly limited
  - ☐ Not at all limited
5. During the past two weeks, **my legs felt tired or weak....**
  - ☐ All of the time
  - ☐ Most of the time
  - ☐ Much of the time
  - ☐ Some of the time
  - ☐ A little of the time
  - ☐ Hardly any of the time

- ☐ None of the time

6. During the past two weeks, because of the poor circulation in my legs **I have been restricted in spending time with my friends or relatives....**

- ☐ All of the time
- ☐ Most of the time
- ☐ Much of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

7. During the past two weeks, **I have had pain in the foot (or leg) after going to bed at night**

- ☐ All of the time
- ☐ Most of the time
- ☐ Much of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

8. During the past two weeks, **pins and needles or numbness in my leg (or foot) have caused me....**

- ☐ A very great deal of discomfort or distress
- ☐ A great deal of discomfort or distress
- ☐ A good deal of discomfort or distress
- ☐ A moderate amount of discomfort or distress
- ☐ Some discomfort or distress
- ☐ Very little discomfort or distress
- ☐ No discomfort or distress

9. During the past two weeks, **the distance I can walk has improved....**

- ☐ Not at all—check this if the distance is unchanged or has decreased
- ☐ A little
- ☐ Somewhat
- ☐ Moderately
- ☐ A good deal
- ☐ A great deal
- ☐ A very great deal

10. During the past two weeks, because of the poor circulation in my legs, **my ability to walk has been....**

- ☐ Totally limited, couldn't walk at all
- ☐ Extremely limited
- ☐ Very limited
- ☐ Moderately limited
- ☐ A little limited
- ☐ Only very slightly limited
- ☐ Not at all limited

11. During the past two weeks, **being (or becoming) housebound has concerned me....**

- ☐ A very great deal
- ☐ A great deal
- ☐ A good deal
- ☐ Moderately
- ☐ Somewhat
- ☐ A little
- ☐ Not at all

12. During the past two weeks, **I have been concerned about having poor circulation in my legs....**

- ☐ All of the time
- ☐ Most of the time
- ☐ Much of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

13. During the past two weeks, **I have had pain in the foot (or leg) when I am resting**

- ☐ All of the time
- ☐ Most of the time
- ☐ Much of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

14. During the past two weeks, because of the poor circulation in my legs, **my ability to climb stairs has been....**

- ☐ Totally limited, couldn't climb stairs at all
- ☐ Extremely limited
- ☐ Very limited
- ☐ Moderately limited
- ☐ A little limited
- ☐ Only very slightly limited
- ☐ Not at all limited

15. During the past two weeks, because of the poor circulation in my legs, **my ability to participate in social activities has been....**

- ☐ Totally limited, couldn't socialize at all
- ☐ Extremely limited
- ☐ Very limited
- ☐ Moderately limited
- ☐ A little limited
- ☐ Only very slightly limited
- ☐ Not at all limited

16. During the past two weeks, because of the poor circulation in my legs **my ability to do routine household work has been....**

- ☐ Totally limited, couldn't perform housework at all
- ☐ Extremely limited
- ☐ Very limited
- ☐ Moderately limited
- ☐ A little limited
- ☐ Only very slightly limited
- ☐ Not at all limited

17. During the past two weeks, **ulcers or sores on my leg (or foot) have caused me pain or distress....**

- ☐ All of the time
- ☐ Most of the time
- ☐ Much of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time- (pick this one if you do not have leg ulcers)



18. Because of the poor circulation in my legs, **the range of activities that I would have liked to do in the past two weeks has been....**

- ☐ Severely limited—most activities not done
- ☐ Very limited
- ☐ Moderately limited—several activities not done
- ☐ Slightly limited
- ☐ Very slightly limited—very few activities not done
- ☐ Hardly limited at all
- ☐ Not limited at all—have done all the activities that I wanted to

19. During the past two weeks, **problems caused by poor circulation in my legs has made me feel frustrated....**

- ☐ All of the time
- ☐ Most of the time
- ☐ Much of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

20. During the past two weeks, **when I have had pain in the leg (or foot) it has given me....**

- ☐ A very great deal of discomfort or distress
- ☐ A great deal of discomfort or distress
- ☐ A good deal of discomfort or distress
- ☐ A moderate amount of discomfort or distress
- ☐ Some discomfort or distress
- ☐ Very little discomfort or distress
- ☐ No discomfort or distress

21. During the past two weeks, **I have felt guilty about relying on friends or relatives**

- ☐ All of the time
- ☐ Most of the time
- ☐ Much of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

22. During the past two weeks, because of the poor circulation to my legs, **my ability to go shopping or carry bags has been....**

- ☐ Totally limited, couldn't go shopping at all
- ☐ Extremely limited
- ☐ Very limited
- ☐ Moderately limited
- ☐ A little limited
- ☐ Only very slightly limited
- ☐ Not at all limited

23. During the past two weeks, **I have worried I might be in danger of losing a part of my leg or foot....**

- ☐ All of the time
- ☐ Most of the time
- ☐ Much of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

24. During the past two weeks, **the distance I can walk became less**

- ☐ A very great deal
- ☐ A great deal
- ☐ A good deal
- ☐ Moderately
- ☐ Somewhat
- ☐ A little
- ☐ Not at all—check this if the distance is unchanged or has increased

25. During the past two weeks, **I have been depressed about the poor circulation in my legs....**

- ☐ All of the time
- ☐ Most of the time
- ☐ Much of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

**This is the end of the questionnaires, thank you for participating.**

## **SHORT FORM MCGILL PAIN QUESTIONNAIRE-2**

- **Please complete the following questionnaire relating to the pain you feel when you walk**

## Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2)

This questionnaire provides you with a list of words that describe some of the different qualities of pain and related symptoms. Please put an **X** through the numbers that best describe the intensity of each of the pain and related symptoms you felt during the past week. Use 0 if the word does not describe your pain or related symptoms. (SF-MPQ-2 © R. Melzack and the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), 2009. All Rights Reserved.)

<b>1. Throbbing pain</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>2. Shooting pain</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>3. Stabbing pain</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>4. Sharp pain</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>5. Cramping pain</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>6. Gnawing pain</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>7. Hot-burning pain</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>8. Aching pain</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>9. Heavy pain</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>10. Tender</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>11. Splitting pain</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>12. Tiring-exhausting</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>13. Sickening</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>14. Fearful</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>15. Punishing-cruel</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>16. Electric-shock pain</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>17. Cold-freezing pain</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>18. Piercing</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>19. Pain caused by light touch</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>20. Itching</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>21. Tingling or 'pins and needles'</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				
<b>22. Numbness</b>	<i>none</i>	<table border="1"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	0	1	2	3	4	5	6	7	8	9	10	<i>worst possible</i>
0	1	2	3	4	5	6	7	8	9	10				

## **PATIENT GLOBAL IMPRESSION OF CHANGE SCALE**

- Please answer the following questions in relation to how you feel since starting to use the TENS device

Patients’ Global Impression of Change (PGIC) Scale

Since starting to use TENS, how would you DESCRIBE THE CHANGE (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS and OVERALL QUALITY OF LIFE, related to your peripheral arterial disease? (tick ONE box).

- No change (or condition has got worse)

☐ 1
- Almost the same, hardly any change at all

☐ 2
- A little better, but no noticeable change

☐ 3
- Somewhat better, but the change has not made any real difference

☐ 4
- Moderately better, and a slight but noticeable change

☐ 5
- Better, and a definite improvement that has made a real and worthwhile change

☐ 6
- A great deal better, and a considerable improvement that has made all the difference

☐ 7

In a similar way, please circle the number below that matches your degree of change since starting to use TENS:

Much Better					No Change						Much Worse
0	1	2	3	4	5	6	7	8	9	10	

#### 14.19: APPENDIX 19: FOCUS GROUP ANALYSIS

PAD and IC				
Meaning units	What is it about?	What does it mean?	Sub-themes	Themes
P5 you just have to put up with it because you will get it, you will get the pain every day so you just have to get used to it, put up with it	There is no other option for them other than enduring the pain because there is no cure	Acknowledgement but not necessary acceptance of the chronic nature of the disease- they have to 'put up with it' – negative connotations rather than 'get on with life'?	Acceptance	Acceptance, adaptation and control of the pain and disease
P3 that's your tablet is it? That's your simple cure- just stop walking and there is no pain	Stopping walking is easy to do and takes the pain away	There is a simple cure for their pain and they can employ it whenever they want. If the pain goes away so easily when you stop walking why isn't there an easy cure for it?	Control	Acceptance, adaptation and control of the pain and disease
P5 you have got to stop, ..... your mind is saying to you, 'stop and it will go away if you stop' ..... that's right, it does go away yeah so you say to yourself, what's the point	They describe the reasoning in their mind while walking: if they stop, the pain <u>will</u> go away, if they keep going, it will continue. The mind always resorts to stopping as this is common sense therefore they find it hard to push their walking further.	When they weigh up the benefits of walking in pain in their mind, the choice to stop always wins as they don't see the point of continuing or they just want the pain to go away and they have a simple cure?	Control	Acceptance, adaptation and control of the pain and disease
P2 but even before it is sore I think if you are walking you are very conscious of knowing, now I can get a seat just along there or there or I have seen me go into a shoe shop because they have the bits you can sit to try on shoes, I'm no trying on shoes, I just need a seat	The planning and thinking about when they will next get a seat dominates their mind when walking and they are constantly trying to find opportunities to stop and make it look normal	Constantly thinking about the pain and how they are going to manage an ambulatory situation. They try to do this in as 'normal' a way as possible i.e. shoe shop, because they are embarrassed by having to stop and want others to think they are normal.	Coping	Acceptance, adaptation and control of the pain and disease
P5 I've not changed, you just get on with it and that's it. You get used to it ken	They have not changed their lifestyle, rather they are just coping with it	Their limitations are not severe enough to warrant a change in lifestyle. They feel strong enough to manage	Control	Acceptance, adaptation and control of the pain and disease

P1 one of them said to me, 'I don't know how you can play golf' but you have just got to, if you want to get on with your life you just have to do these things	They have managed to accept the changes to their life and can therefore get on with it. They have noticed that others have not yet reached this point.	With appropriate advice and education patients are able to accept and adapt to this chronic condition.	Coping	Acceptance, adaptation and control of the pain and disease
P2 when I am doing the ironing and things like that when you are standing you know for a while, and you have got to, you know the washing and ironing is done in small lots so you are not faced with a huge pile and standing for ages and I certainly can't do any gardening, I've had a gardener for quite some time but I couldn't do it	They have to alter the way they tackle tasks so that they can manage them - pacing	Independently altering ADLs so that they can manage to complete the same tasks. Managing their own coping strategies	Coping	Acceptance, adaptation and control of the pain and disease
P2 I couldn't even contemplate having a dog now because I wouldn't be able to walk it	Unable to maintain previous lifestyle due to pain and decreased walking ability	Self-selecting to opt out of activities. QoL limited due to decreased walking ability and pain	Physical limitation	Acceptance, adaptation and control of the pain and disease
P1 well em, not particularly. I can walk on golf courses if it is nice and flat and it is soft, going for a walk on hard roads is a problem for me and climbing up hills	Environment but surface and gradient especially affects the distance they are able to walk	Different environments mean more or less walking ability. When encouraging walking, need to take environment into consideration	Walking ability	Acceptance, adaptation and control of the pain and disease
P1 I don't think there is very much I can do about it .... well, what they told me was my problem is inoperable and em, the best thing I can do is walk as much as possible	Lack of treatment options. Walking might help the disease	Lack of control. Walking as a coping mechanism/way to take control	Control	Acceptance, adaptation and control of the pain and disease
P3 if what you are doing is going to help in the future. I can't see you getting a pill that will cure it, obviously it is going to be something surgical I would imagine	Someone will find a cure for their disease / pain and it will be passive (surgical).	Unrealistic hope / understanding of the chronic, progressive nature of the condition.	Control	Acceptance, adaptation and control of the pain and disease



P4 You look back and the things I have got to take I think I am taking these because the doctor says to take them but is it making any difference? Say if I was to stop them, would it make it worse?	They are unsure if the medications they are taking are making much difference	They do not know completely the reasons for taking the medications and their effects and thus are not sure about complying with them. However, they have accepted that the doctor must be correct and therefore keep on taking them	Control	Acceptance, adaptation and control of the pain and disease
P5 only comment is that you just have to put up with it because you will get it, you will get the pain every day so you just have to get used to it, put up with it	There is no other option for them other than enduring the pain because there is no cure	Acknowledgement but not necessary acceptance of the chronic nature of the disease- they have to 'put up with it' – negative connotations rather than 'get on with life'? They are indicating that they know there is nothing that can be done about their pain. They express it in a negative manner 'put up with it', 'get used to it'	Acceptance	Acceptance, adaptation and control of the pain and disease
P5 because I don't want to sit in that house, ken what I mean? ..... no way, so you just have to put up with it. P4 yep, the worlds always saying to me 'grin and bear it'.... P2 'grin and bear it'. P5 exactly. P4 and that's been happening for 6 years, 'grin and bear it'	They don't want to accept the lifestyle limitations so they continue on and 'put up, with the pain	They are motivated to keep mobilizing and continue with as many ADLs as possible, despite the pain.	Acceptance	Acceptance, adaptation and control of the pain and disease
P2 no Paracetamol is what they say ..... I might as well have a couple of sweeties ..... I cant have anything stronger than paracetamol because of the other things I am on but I might as well have a sweetie for all the good it does, it doesn't make any difference	Current treatment or advice for treatment of pain is insufficient and does not work	They feel their pain is not understood and under-treated. They feel the treatment options for their pain are limited by the other medications they are on. They feel that treatment for pain is primarily medical.	Control	Acceptance, adaptation and control of the pain and disease
P5 I've not changed, you jut get on with it and that's it. You get used to it ken	They have not changed their lifestyle, rather they are just coping with it	Their limitations are not severe enough to warrant a change in lifestyle. They feel strong enough to manage	Coping	Acceptance, adaptation and control of the pain and disease

P4 it is, they keep saying 'grin and bear it' and that's all I have been doing for years and years now. P5 yeah, me too, the very same. I'm just like, it will be 5 year, maybe 6 years I have had it and you just have to put up with it.	The lack of advice or treatment options for the pain / disease and the fact that they are just told to get on with it.	They are expressing frustration at the lack of options there are to reduce the pain /treat the disease.	Frustration	Acceptance, adaptation and control of the pain and disease
P4 as soon as they say you could lose your leg that's me, forget about it, grin and bear it	They will not accept the risks of surgery to gain a reduction in pain- not severe enough.	They can cope with the level of pain they are in and would not risk losing a leg	Risks and benefit	Acceptance, adaptation and control of the pain and disease
P4 you know you think what the hell is the matter because one you stop as you said, once you stop the pain is gone ..... that's what puzzling me all these years and it has been going on almost 10 years now and I keep saying to the surgeon and all that and they said we could tell you what the problem is and we could fix it but we don't know what the problem is so all this is probably helping. But it is frustrating the problem you know is just in here ( <i>points to head</i> ) you just have to grin and bear it	They don't know what the problem is and why the pain goes away when you stop walking. They don't believe the surgeon knows what is happening either and there are no treatment options. They feel treatment is just general things that all 'might' be helping in some way. They feel the problem is psychological to some degree.	They feel as though no one understands what is wrong with them and therefore there are no treatment options, only 'general' things to stop the pain getting worse.	Treatment options	Acceptance, adaptation and control of the pain and disease
P5 when it goes away you are like, well fine but when you go away again back it comes again so you stop again. That is, it is more frustrating than anything	Pain is not too severe, just frustrating as it keeps coming back.	The intensity of the pain is not too bad; they are more affected by the recurrent nature. In some ways it would be better if the pain was worse?	Transient pain	Frustration

P4 that's the worst part of this bloody pain, it's the frustration of the pain ..... it's not going to kill you but it is really debilitating ..... the thing is its sore but once you stop, its gone ..... that's what puzzles me all the time ..... you think, oh god and you sit down and all of a sudden, bang and its not there	The fact that the pain is not that severe but it is there every time they walk however, when they stop, it goes away. They are confused as to the mechanisms involved	The lack of knowledge about the disease and the mechanisms of the pain result in frustration. The pain is of a manageable type when present i.e. they do not walk until it is so severe that they cannot tolerate it however, the worst part of the pain is that it always comes back	Transient pain	Frustration
P4 But as I say they say 'grin and bear it' but this has been going on for years and years for me, its like having a leg off-grin and bear it so you just, what can you do?	They have just been told that they need to get on with it and there is nothing that can be done for them however, they feel that experiencing the pain in the leg is like having a leg off	They are frustrated at the lack of treatment options and find it hard to endure the pain	Grin and bear it	Frustration
P5 there is only one thing that takes the pain away and that is when you sit down ..... that takes the pain away ..... and the frustrating thing is you only have to sit for half a minute if at that and it is away. Then you walk again an it comes back	When they sit down the pain goes away, that is the only method of effective pain relief they have found. However, it is frustrating when they walk again, the pain comes back	They know that resting relieves the pain however, the fact that it comes back after the promise of relief might even be worse than if it hadn't gone away in the first place?	Transient pain	Frustration

<p>P5: the same as when you are walking to the football with them we have got a good bit, maybe, hmm I don't know, 20 minute walk from the ground to the bus well, I'm like, miles behind them cause I cannae keep up with them ken what I mean. And even a lot of them are a lot older than me and they can ..... and you say to yourself 'how?' it's the most annoying thing but once I stop like, I just need a minute and away I go again and its fine for maybe another couple of minutes then I have to stop again. That's the most frustrating thing about it- you have got to stop.</p>	<p>Expressing annoyance at lack of walking ability and resultant social limitations. Expressing frustration about having to stop walking all the time and embarrassment of falling behind friends</p>	<p>Frustrated at reduction in mobility. Frustration at it being such an overt issue i.e. if they could hide the pain it would be much better</p>	<p>Social limitation</p>	<p>Frustration</p>
<p>P4 you are a nuisance to them .... cause you are taking so long ..... it is, that's the worst part about this pain, it's the frustration</p>	<p>They feel their disease is affecting other people and this is embarrassing and frustrating. It is the lack of walking ability that is causing this.</p>	<p>Decreased walking ability leads to feelings of frustration as they feel this is affecting others as well as themselves. They feel frustrated about the feelings of frustration- ? NOT FAIR?</p>	<p>Social limitation</p>	<p>Frustration</p>
<p>P4 and it is that bloody frustration and then you think you will not bother coming the next time, I am just stuck indoors now and I can't even go out in the garden to help the missus and she's like get yourself indoors, it's that frustrating, its not the pain. Its just up here (<i>points to head</i>) it's not the pain</p>	<p>They experience frustration at their lifestyle limitations rather than because of the pain- it is the pain causing the issues but it is the social limitations that they focus on</p>	<p>Frustration due to reduced ability to continue with daily life is their main issue rather than the pain</p>	<p>Social limitation</p>	<p>Frustration</p>

P4 its like when you say, you're walking and when you stop and you sit down for 2 minutes and it gone and you think, that's fine, and you get up again and it starts again. That's what nobody has ever said to me, this is what's happening with this disease, because it <u>is</u> a disease. Well you say it is there one minute and it is gone the next, you get up again and its come again, so but they have never explained to me what it is	Pain is present when walking but goes away when you stop. When you start walking again it comes back and nobody has explained why this happens or what is happening in the legs. It is being treated as a 'condition' not a disease	They feel that their symptoms are not fully understood because it has not been explained properly to them. They don't fully understand what is happening when they feel pain. This may enhance or contribute to pain-related fear (fear of the unknown damage?)	Education	Knowledge and understanding
P4 the thing is you bleeding, you just think you can go on a bit more, a bit more and then you say no I can't and you stop and the pain is gone ..... Its funny, you know you can't explain it to people what it is like unless they have had it you know like you	The fact that when they stop walking the pain goes away and it is this that others do not understand	They feel that their disease is not fully understood by those around them and this is partly due to the transient nature of the pain	Others understanding	Knowledge and understanding
P5 the pain is telling you to stop	They are sharing their pain beliefs that it is a signal to stop walking	This indicates a lack of understanding of the pain but also very normal pain behaviour/ beliefs	Attitudes and beliefs	Knowledge and understanding
P3 its not permanent damage, you are not doing it permanent damage because eventually you will stop but if you pushed how far, you have done the treadmill you stop there because you are frightened to go a bit further because you don't know what you are doing to yourself	This participant has slightly more understanding of the pain mechanisms and has developed an understanding that the pain cant be indicating permanent damage as they have had it for so long and not much has changed. However, the still accept that you are frightened to push it further just in case.	This demonstrates the confusion and conflict of education, attitudes and beliefs these patients face. They have reasoned well that the pain cannot be causing permanent damage however they are still frightened to push it 1. Because it is pain and 2. Because no one has told them that this is ok/ described exactly what is happening and alleviated their concerns	Attitudes and Beliefs	Knowledge and understanding

P1 if I'm told by my doctors anyway without the TENS machine that the more I walk, the better chance I have of my pain maybe dissipating a bit	Walking more might reduce pain	Walking is a way of controlling the pain and possible treatment	Benefits of waking	Knowledge and understanding
P3 if it is going to stop it getting worse, that's what I am doing, I will keep doing it. Obviously, you would like a cure for it but its not going to happen overnight is it?	Walking is a treatment but not a cure for the pain / disease	Walking might help control pain but wont cure it. Willing to try interventions that might just help them a little bit	Control	Knowledge and understanding
P4 there is nothing you can do to change it. P5 yeah, well that's what I think, that's my theory as well	They think there is nothing they can do about the pain they experience	They feel that they have no control over the pain and disease progression. They are employing passive coping strategies?	Control	Knowledge and understanding
P4 yeah, well the pills they give you the day are not going to cure you but it is going to help to lessen the pain ..... you know it helps towards the, but it is not going to cure it	They think the medication is helping lessen the pain so they continue taking them. They say they would do something just to stop it getting worse but then talk in terms of improvement	They realise they may not be cured (passive attitude) however; they think that the pain may lessen if they continue to take the pills. This shows hope and maybe poor understanding or bad advice? Rather than thinking that they might improve, they need to be counselled to expect just to not get worse too quickly?	Control	Knowledge and understanding
P4 if they could explain to you what is causing the pain and if they say look, we cant give you anything, well they cant give you anything to get rid of the pain, maybe it helps ease the pain but you cant get rid of it. If they could explain to you what's happening and you could say oh, fair enough then	Healthcare staff not knowing or being able to explain what is happening	They feel that nobody understands what is happening to them or if the medical staff know, they do not explain it properly to them.	Education	Knowledge and understanding

P5 and its alright for the doctor to say 'loose weight, that will help' but I'm not a big eater anyway so my biggest problem is cheese but I'm no gonna want to stop a things that I love just because the pain because how should I? I like to go for a pint at the weekend with the boys, I'm no gonna stop it ..... because I don't want to sit in that house, ken what I mean?	Not changing lifestyle because of the pain. They don't feel that loosing weight will make much difference to pain / disease. Not willing to make changes to eating habits as they don't see that it will help them very much.	They don't see the link between weight control, eating and their disease. They see it only as a pain that should be able to be cured and they can continue with their lives. Need information and education about the disease and how risk factor modification can help and what changes to expect and really why they need to do it. Not just about the pain- what the disease process signals.	Education	Knowledge and understanding
P1 because the chances are the more you walk the blood vessels sometimes kick into play ..... that's what I have been told. And I think that my playing golf bears that out because there are some days when I feel a bit of pain and it doesn't last maybe more than a few minutes and you keep walking and it goes away. It comes back again but it does seem to come and go	This participant understands the reasons to walk and how walking can make the disease / pain better and therefore walks for exercise / treatment.	With correct education and information patients will comply with the advice given and be motivated to walk. When they know what it is doing, walking can be employed as a coping strategy/ treatment and method to achieve acceptance/ adaptation	Education	Knowledge and understanding
P3 I have only got it in one leg but I presume if I hadn't taken the medication it would have spread to the other leg? P3 it is my right leg that bothers me too. If I hadn't have stopped the smoking, would it have got worse?	They have an idea that their condition might have been worse if they hadn't been taking medications / stopped smoking	They do have an appreciation of the progressive, chronic nature f their condition but are not sure about it.	Education	Knowledge and understanding

P5 that's what he said to me, the only option is surgical, well that was like 2 years ago and I don't know if anything has changed now but that was the only thing he said to me would help was that thing like you said ..... the stent or taking another bit out of my leg and putting it in but he said that is the last option	The options they have for treatment of the pain/ disease- they have been told that the only option s to have surgery.	Firstly, they have the perception that their condition is treatable / acute rather than a chronic, progressive condition for which there is no cure. Secondly, they are left with the perception that they have no control over their disease and the only person who can do anything for them is the surgeon.	Education	Knowledge and understanding
P3 I have to take one too but it's a preventative measure	This patient understands the true purpose of the medications and is therefore more positive about them	With correct expectations of outcomes come compliance and more positive psychological factors	Expectations	Knowledge and understanding
P4 the thing is you bleeding, you just think you can go on a bit more, a bit more and then you say no I can't and you stop and the pain is gone ..... Its funny, you know you can't explain it to people what it is like unless they have had it you know like you	The fact that when they stop walking the pain goes away and it is this that others do not understand	They feel that their disease is not fully understood by those around them and this is partly due to the transient nature of the pain	Others understanding	Knowledge and understanding
P5 that's what I'm saying, other people dinnae understand what the pain that you go through, ken what I mean?	Other people don't understand the pain they endure	They feel that other cannot understand the pain they experience as it is unlike any other experience of pain	Others understanding	Knowledge and understanding



<p>P3 and they have tried that treadmill with putting all the things on you and that and the lad explained at the time, its not going to cure you, we are researching it now to see what it is, and until you find out what is causing it but they already told me its the narrowing of the arteries that's causing it and basically the smoking is causing that. So there is not really a cure for it is there? Unless they take an artery out and replace it and I don't see that happening. I mean and you get to our age, well not P5 but myself like, is it worth the while? Just put up with the pain I certainly wouldn't rush along for it (<i>surgery</i>). P5 no way, you just put up with it</p>	<p>Firstly they perceive that the previous research study was to find out what was happening with them. They understand what is causing their pain and that there is not a cure for it at present unless they do bypass surgery. They then go on to say that surgery is not worthwhile due to the risks involved for minimal benefit at their age.</p>	<p>This participant is aware of the physiological mechanisms of the disease and the prognosis. They are in agreement that they wouldn't risk surgery for the 'minimal' pain they experience at present. They do not feel the disease has such an effect on their lives that they would risk surgery for a reduction in pain</p>	<p>Education</p>	<p>Knowledge and understanding</p>
<p>P4 You look back and the things I have got to take I think I am taking these because the doctor says to take them but is it making any difference? Say if I was to stop them, would it make it worse?</p>	<p>They are unsure if the medications they are taking are making much difference</p>	<p>They do not know completely the reasons for taking the medications and their effects and thus are not sure about complying with them. However, they have accepted that the doctor must be correct and therefore keep on taking them</p>	<p>Control</p>	<p>Knowledge and understanding</p>
<p>P5 see the likes of when you have to carry on you try to keep up with them (<i>football crowd</i>) ..... you start walking like all kind of funny like you have done the toilet in your pants, but you do because my brother has said to me many times.</p>	<p>Their walking pattern changes when in pain and this is embarrassing for them in social situations. Also, this is when it normally happens as they are trying to keep up</p>	<p>The pain experience is characterized by embarrassment and frustration in a social setting</p>	<p>Walking ability</p>	<p>Limited physical and social functioning</p>

P2 this is what makes it frustrating you see if you are going to go out with somebody. You know they want to take you here, there or wherever but I mean you know that you are gonna have them stop every wee bit and they don't need to stop	The fact that the pain limits their ability to participate in social activities due to them having to stop all the time. They feel frustrated / embarrassed about having to stop when their friends don't have to	The disease / pain causes them embarrassment when participating in social activities. Fear of embarrassing themselves/ being a burden on their friends and family	Transient pain	Limited physical and social functioning
P2 to come and do something, the first thing you think of is how much walking is involved ..... and will I just be a damned nuisance if I go because I will be trailing back and behind the others .... you know? And you just don't go	When there is an opportunity to participate in a social activity they have to think about how much walking they will need to do as if it too much they will not go. This is because they feel they are a nuisance. They decide not to participate themselves as they are worried that their friends will become frustrated with their decreased walking ability	Their pain limits their participation in social activities and it is directly related to walking ability, not degree of pain	Social activities	Limited physical and social functioning

<p>P4 it's the same on the golf course, I've had to give up golf because you cannae, you cannae get, you pay to play 18 holes and you cannae get round, you get round about 8 and that's it, and your mates are saying 'come on' and you say I wish I could come on but that's it and so I've stopped playing the golf and I've taken the bowling up and that's helped me a hell of a lot, the bowling, and that 3 days a week for about 2 hours and I really look forward to that and funny enough when you are on there bowling from the car to the bowling green your pain is there but once you get on the bowling green it is gone</p>	<p>This patient is describing how their decrease in walking ability has limited their participation in hobbies- they have had to give up golf but they can still play bowls.</p>	<p>This shows an ability to adapt to their limitations and motivation to make the most of the abilities they have.</p>	<p>Social activities</p>	<p>Limited physical and social functioning</p>
<p>P3 you know it is going to get worse ..... it would be interesting to try to go further just to see what damage you would do but then it is too late by then</p>	<p>They think that if they walk past the point they normally stop and experience more pain it will cause them damage</p>	<p>They are displaying fear of pain behaviours and beliefs relating to their pain so telling them to walk further into their pain without any more education and information would not necessarily be efficacious</p>	<p>Fear</p>	<p>Pain</p>
<p><i>CS so say for now, I want you to just think about your health in general, what first jumps into your mind, what's the first thing you think about?</i> P2 the pain in my leg. P5 the leg, exactly. P2 it stops you doing everything really. P5 that's the only thing really, thing that bothers me, is the legs. (General agreement)</p>	<p>The pain is the main focus of the health self-image. When they think of their disease, they think of their pain</p>	<p>Pain is the defining factor of the disease rather than the general systemic arterial disease. They are focusing on the impairment and maybe this is related to healthcare provider actions</p>	<p>Disease perception</p>	<p>Pain</p>

P3 Paracetamol is what they say (General laughter) P3 I might as well have a couple of sweeties ..... I cant have anything stronger than paracetamol because of the other things I am on but I might as well have a sweetie for all the good it does, it doesn't make any difference	Pharmaceutical pain relief is no good because they cant take any strong painkillers due to the possible interactions with their other medications / possible kidney/liver damage and the basic painkillers have no effect	Developing further pharmaceutical interventions is limited due to the possible interactions etc. They feel they need strong painkillers but these are not necessarily suitable as they don't have the pain al the time	Treatment options	Pain
P2 the pain in my leg ..... it stops you doing everything really	Their perception of lifestyle limitations due to the pain is large- everything	This patient feels that the pain is stopping them from participating in everything meaning ADLs and social activities	Physical limitation	Pain

TENS				
Meaning units	What is it about?	What does it mean?	Sub-themes	Themes
P1 I certainly found that, I will tell you how much I found how good, I have already been out and ordered, not that I have used them but I have ordered myself some new pads	They found TENS to be so effective that they are going to continue to use it independently and have already spent their own money on getting more equipment	They have a lot of confidence in TENS and they feel it has helped them enough to want to continue using it. Along with this, they are so confident that they are willing to purchase their own equipment	Benefit	Control
P5 I would say it is easy to use but I don't think it is any good for the disease, well that's just my personal opinion, it didn't do me any good, well the pain was still there when I was using it	The device was easy to use however, it didn't take the pain away completely therefore was assessed to be ineffective	TENS was simple to use and reduced the pain experienced. However, due to the participant's expectations since it would take the pain away completely, they felt it was not effective and therefore would not use it.	Benefits	Expectations
P5 I still definitely got the pain with it when I did use it, did you P3? P3 oh aye. Aye. I still had it but it was a different form of pain P5 right P3 it was sort of numbing, not so sore but it was still there P2 I didn't feel that this sort of alleviated the pain at all, I was aware of the pulsing as you are saying but to me it wasn't making things any better	Mixed feelings and experiences of the participants from using TENS. One felt that it changed the nature of the pain in a positive way. Another was unsure as hadn't used it much and expressed interest in how it worked for the other participants. The last participant didn't feel that it helped at all- they felt the pulsing but did not feel it reduced the pain experienced	Different participants had different experiences of using TENS and its effectiveness at reducing pain. This could be due to their expectations, the severity of their disease, their use of the device, peripheral neuropathies or other psychological and/or physiological factors.	Masking the pain	Expectations
P3 my friend, she bought one, they told her it was a frozen shoulder, she bought one out of the chemist and was using it for about three weeks and she said, perfect, it worked perfect for her. She saw that one likes and the one she got was a lot smaller and she used it for 15 minutes in the morning and 15 minutes at night, shoulder is gone. She has had these	This participants friend used a TENS machine for their frozen shoulder with good results. They thought the one they had was a lot smaller and they bought it from the pharmacy and use it for 2 x 15mins per day	If they have heard of someone else using TENS and getting benefit they are more willing to try and likely to get positive results as they believe in the treatment.	Beliefs	Expectations

injections and that and they didn't do anything for her, so I mean, it must be good isn't it?				
P1 I met a friend, a girl on the golf course and she, somebody had told me she had a TENS machine and I spoke to her and she has got some Japanese, I cant remember what it is called but she found it on the internet and she must be the same sort of thing as the Japanese one, probably a wee bit more sophisticated than the TENS machine because I think she said she paid £70 for it but it has obviously got pads and she uses it for her back and she has found it good	This participant's friend uses a similar device for their back with good results. The participant thinks it might be something more complicated as it costs £70 and is from Japan.	Something exotic and expensive has been found to be effective by one of their friends and thus their expectations of TENS are raised and they are possibly more willing to give it a try and be ready to experience positive effects.	Beliefs	Expectations
P3 I still had it ( <i>the pain</i> ) but it was a different form of pain ..... it was sort of numbing, not so sore but it was still there	They still felt the pain however, the TENS had changed it's quality and intensity	TENS was effective in changing the pain experience. The participant reported a change in quality of pain as well as intensity. It however, was not completely effective again and thus not reported as favourable due to differing expectations	Sensation	Pain
P3 yeah, it sort of numbed the pain, more concentrated, you know instead. The tingling takes it away right away, the initial pain. It was definitely as I say if, it has got potential; it is working on the right lines, its not taking the pain away, just covering it	They felt that the TENS numbed the pain and the stimulation takes the pain away immediately at the pain threshold level. This however, didn't last and they experienced pain and tolerance eventually but they feel it is working	This participant reports that it 'numbed' their pain and thus was effective but not quite enough- they feels that it is a good intervention and has promise for helping with the disease/ pain	Masking the pain	Pain

P1 a golf course that is quite difficult to walk and I used it and I did have some pain but certainly nothing like what I would have expected to experience.	TENS reduced the amount of pain experienced when performing a hobby and thus they were able to perform the said hobby- something they would not be able to do before	The TENS machine is effective at reducing the pain experienced for this patient and allowed them to complete their hobby	Masking the pain	Pain
P3 it numbed the pain, you maybe walked a wee bit further. I did notice a couple of times my foot went numb when I had the machine on. Well that has happened before without the machine but it seemed to come on a bit earlier	The TENS machine numbed the pain and allowed them to walk a bit further than normal.	TENS is effective in reducing the pain experienced apparently through gating mechanisms? This helped to prolong time to pain tolerance.	Walking ability	Pain
P2 yes, I put it on in the morning and had it on all day P4 I used it three times a week for 3 hours up and down between the bowling green P5 no for me, I used it once a week because that's the only time I go walking	They all used the device in different ways depending on their normal ADLs.	Patients may just use it to help make their normal activities easier rather than increasing their level of activity?	TENS use	Physical and social functioning
P1 I find I could get round when I am using it now this is a golf course that is quite difficult to walk and I used it and I did have some pain but certainly nothing like what I would have expected to experience. So to answer your question I would say that the TENS machine definitely lessens the pain whether I could, I can't definitively say that it totally takes the pain away.	TENS allowed this participant to play this particular golf course that they would have normally struggled with significantly less pain	TENS reduces the pain experienced, helps to improve walking ability and this allows them to participate in social activities / hobbies with less discomfort	Social activities	Physical and social functioning
P1 if I didn't have the TENS and this particular course I'm thinking, I could never get round that course without stopping and having to shake my leg and wait a minute which becomes quite embarrassing when you are playing with someone and you are holding them up	TENS helps them complete an activity which in turn means they suffer less embarrassment	The TENS machine is effective in reducing pain and increasing performance. This results in and reduction in the embarrassment of needing to stop/ disease limiting function	Walking ability	Physical and social functioning

P1 it means I could walk further if I wanted to.	TENS allowed them to walk further if they needed to	TENS helps to increase walking ability	Walking ability	Physical and social functioning
P3 every day, maybe not so much at the weekends but during the week and I didn't put it on today because I was coming here. I would put it on in the morning and take it off at night and when I needed it I switched it on	They put the TENS machine on in the morning and wore it all day during the week when at work etc. they didn't wear it as much at the weekends- doing less activity?	Participants use the TENS device all day and as instructed and found this to be ok. They maybe wear it less when doing less activity	TENS use	Usability
P1 I don't think there is any way that I could think to be improved just the fact that if it is on your legs, you have got to put the wires up through your trousers and then gets onto your belt so	There is no way that they can think to improve the TENS unit except possibly making it wireless	TENS is relatively easy to use and unobtrusive however, it would be better if there were no wires/ nothing to hang on belt	Technical specifications	Usability
P3 even adults were querying what it was. I am willing to try anything P2 that's true, I'd try anything as well whatever might work	People would notice the device on their belt and think it was strange/ they were embarrassed that people noticed it. Despite this, they were not too bothered as they are desperate to find a solution for their pain and don't mind some embarrassment	Need to refine the design and possibly use wireless TENS to avoid patients not using it due to embarrassment. They will work hard and sacrifice some embarrassment to find a solution for their pain.	TENS use	Usability
P5 the thing about it for me was the tingling in my legs with it. I can't bear it P4 oh I didn't mind that, I enjoyed that, the tingling in your legs, aye it helped	One participant disliked the tingling sensation of TENS, another enjoyed it	TENS is not suitable for everyone based on personal preference. This may have affected usage in the current study as well	Sensations	Usability
P1 it means I could walk further if I wanted to. The times I have used it..... I use it now only if I am going to be playing 18 holes of golf, I wouldn't put it on if I had to walk down the street to pick something up at the shop it is quite difficult with me it is on a slight hill when I am walking home I feel a slight pain but I wouldn't put the TENS machine on to do that	TENS helps this participant walk further if he wanted to however, he didn't always use it for short journeys he felt it wasn't required- just put up with the pain. When he was doing anything more, he would use the TENS	When TENS is effective in this participant who uses it selectively and only when he was walking for a prolonged period of time.	TENS use	Usability



P1 is it easy to use? I would say for the majority of people, yes but I am one of these technophobe when it comes to any I find anything like that difficult but that is not to say it, that is only because of me, I think most folk would find it quite simple	TENS is easy to use	TENS is easy to use	TENS use	Usability
--	---------------------	---------------------	----------	-----------

## CHAPTER 15: RELEVANT PUBLICATIONS

---

The following posters relate to the following publications:

**Seenan, C.,** Roche, P.A., Tan, C-W., Mercer, T. 2012. Modification of experimental, lower limb ischemic pain with Transcutaneous Electrical Nerve Stimulation. *Clinical Journal of Pain*. Vol:28(8); pp 693-699

**Seenan, C.,** McSwiggan, S.J., Roche, P.A., Tan, C-W., Mercer, T., Belch, J.F. 2012. McGill Pain Questionnaire Descriptions of Lower Limb Ischaemic Pain in Clinical and Laboratory Settings. Poster Presented at: *The 14<sup>th</sup> World Congress on Pain*, Milan, Italy 27<sup>th</sup>-31<sup>st</sup> August 2012

**Seenan, C.,** McSwiggan, S.J., Roche, P.A., Tan, C-W., Mercer, T., Belch, J.F. 2012. Improved treadmill walking with Transcutaneous Electrical Nerve Stimulation in patients with Peripheral Arterial Disease and Intermittent Claudication. *British Journal of Pain*. Vol:6(2) Suppl. pp 80

**Seenan, C.,** McSwiggan, S.J., Roche, P.A., Tan, C-W., Mercer, T., Belch, J.F. 2012. 'Grin and bear it': patients' experiences of living with Peripheral Arterial Disease and using Transcutaneous Electrical Nerve Stimulation for Intermittent Claudication. *British Journal of Pain*. Vol:6(2) Suppl. pp 81

**Seenan, C.,** Santos, D., Calcraft, J., Weddell, A. Roche, P. A., 2008. Early development of a Lower Limb Ischaemic Pain Test in healthy volunteers using the McGill Pain Questionnaire. Poster Presented at: *The 12<sup>th</sup> World Congress on Pain*, Glasgow, UK 17<sup>th</sup> - 22<sup>nd</sup> August 2008.

# Modification of Experimental, Lower Limb Ischemic Pain With Transcutaneous Electrical Nerve Stimulation

Chris Seenan, BSc,\* Patricia A. Roche, PhD,† Chee-Wee Tan, PhD,‡ and Tom Mercer, PhD‡

**Introduction:** Transcutaneous electrical nerve stimulation (TENS) has been shown to be effective for the reduction of experimentally induced ischemic pain in the upper limb. No studies have been published on the effects of TENS for lower limb ischemic pain.

**Objectives:** To investigate the pain-modifying effect of TENS on experimentally induced ischemic pain in the lower limb.

**Methods:** A modified Submaximal Effort Tourniquet Test-induced ischemic pain in the nondominant lower limb of 27 healthy volunteers. Each of the participants completed a baseline modified Submaximal Effort Tourniquet Test (No TENS) and 1 of the experimental conditions: either high-frequency TENS (HF-TENS) or placebo TENS (P-TENS). The outcome measures were the time taken (in seconds) for the participants to report pain threshold and pain tolerance. Pain endurance was calculated as the difference between these points. Pain intensity during ischemia was assessed using a numerical rating scale. The McGill Pain Questionnaire recorded participants' retrospective description of 'intolerable' induced pain. The differences in scores between these measures at the baseline and TENS intervention was calculated and used for the analysis.

**Results:** Paired Student *t*-tests found significant increases in time to pain tolerance and pain endurance in both the TENS groups ( $P < 0.001$  HF-TENS and  $P < 0.05$  for P-TENS, respectively). When compared with baseline, time to pain threshold increased significantly only with HF-TENS ( $P < 0.01$ ). The independent Student *t*-tests detected greater increases in pain threshold, tolerance, and endurance in the HF-TENS group compared with the P-TENS group ( $P < 0.05$ , 0.002, and 0.003, respectively). Compared with P-TENS, HF-TENS significantly reduced the pain intensity between the fifth and eighth minutes. Both HF-TENS and P-TENS significantly reduced the mean McGill Pain Questionnaire Pain Rating Index scores, but did not show a between-group difference.

**Conclusions:** HF-TENS had stronger modifying effects on several aspects of laboratory-induced ischemic pain than did P-TENS. HF-TENS delayed the onset of pain, reduced pain levels, and delayed the onset of extreme pain over a period of several minutes.

**Key Words:** tourniquet pain test, transcutaneous electrical nerve stimulation, lower limb, ischemic pain, intermittent claudication

(*Clin J Pain* 2012;28:693–699)

Transcutaneous Electrical Nerve Stimulation (TENS) is known to control several types of clinical pain. It also

reduces pain intensity and increases pain endurance in experimentally induced ischemic pain in the upper limb of healthy volunteers.<sup>1–6</sup> No reported studies have tested the degree of pain relief, if any, obtained from applying TENS to induced ischemic pain in the lower limb of standing volunteers using the standardized Submaximal Effort Tourniquet Test (SETT).<sup>1,7–9</sup> If found to be effective in volunteers, TENS could be a candidate for testing on clinical pain in the lower limb associated with ischemic disease. A controlled study of TENS on experimentally induced ischemic pain in the lower limb may identify favorable parameters of TENS stimulation.<sup>1,9</sup> High-frequency TENS (HF-TENS) is reputed to reduce pain intensity, and increase pain tolerance and pain endurance, whereas decreasing the mean McGill Pain Questionnaire (MPQ) pain scores reported with the upper limb SETT.<sup>1,2,6,10</sup> HF-TENS is therefore a first choice candidate for testing on induced lower limb pain.

A series of pilot studies conducted by the authors and their colleagues developed a modified SETT (mSETT) for application to the lower limb. The pilot work also suggested the following:

1. The mSETT provided good test-retest reliability of pain severity and quality.
2. Similarities between volunteers' descriptions of mSETT-induced ischemic pain in the lower limb and SETT-induced ischemic pain in the upper limb, as measured with the MPQ.<sup>11,12</sup>
3. Increased Numerical Rating Scale (NRS) scores of mSETT-induced pain in the lower limb when the position of the participants' was adjusted from supine to sitting, and then into standing positions.
4. A trend toward delayed perception of pain and modified pain scores with applications of HF-TENS.<sup>11</sup>

This study aimed to use the mSETT method and associated pilot study information to compare the effects of HF-TENS and Placebo TENS (P-TENS) on mSETT-induced lower limb ischemic pain in the standing subject.

## METHODS

### Participants

Twenty-seven university student volunteers (16 male; mean age, 27y; range, 19 to 47y) were recruited by email advertising. The researcher explained the experimental procedure and screened the volunteers. The exclusion criteria were

1. Cardiac and neuromuscular disorders (including peripheral neuropathy)
2. Pacemaker
3. Musculoskeletal trauma or surgery in the lower limb
4. Current pain or history of pain in the last 48 hours
5. History of epilepsy
6. Diabetes
7. Pregnancy

Received for publication July 1, 2011; revised November 15, 2011; accepted November 19, 2011.

From the \*Department of Physiotherapy, Glasgow Caledonian University, Glasgow; †University of Aberdeen, Aberdeen; and ‡Queen Margaret University, Edinburgh.

Chris Seenan was the recipient of a Queen Margaret University (QMU) PhD Bursary and this research was conducted at QMU. The authors declare no conflict of interest.

Reprints: Chris Seenan, BSc, School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, G4 0BA (e-mail: chris.seenan@gcu.ac.uk).

Copyright © 2012 by Lippincott Williams & Wilkins

8. Previous use of TENS
9. Medical diagnosis including self-reported psychiatric illness
10. Currently taking any medication.<sup>13</sup>

The study was conducted in accordance with the Declaration of Helsinki and approved by the University Ethics Committee. Written informed consent was obtained from all participants before inclusion.

### Study Protocol

The study was a single-blinded, placebo-controlled, repeated measures experiment. Each participant attended 1 session of approximately 2 hours. The participants were block randomized into either the HF-TENS or P-TENS group. Each participant completed 2 separate episodes of induced pain with the mSETT. One application, the baseline condition, had no intervention. The aim of the study was to examine any change in results between the outcome of the baseline and the experimental condition. The experimental condition was either 1 application of P-TENS or 1 application of HF-TENS. The order of intervention was also block randomized with 50% of the participants in each group completing the baseline condition first (Fig. 1).

### mSETT Procedure

A familiarization session was conducted so that the participants experienced the mSETT procedure and the induced pain (30 s after pain threshold). Questions or issues about experimental technique were addressed before commencing the procedure for the main testing session.

Figure 2 gives a representation of the experimental procedure. The mSETT procedure began with the participant resting supine on a plinth for a 20-min washout period. An elastic bandage (Tubigrip; Size E, Seton Healthcare Group, Oldham, UK) was then applied onto the exposed nondominant lower limb. A sphygmomanometer cuff (20 cm width; Bainbridge, Trimline Medical Products, NJ) was positioned on the nondominant thigh of the participant, 3 cm above the joint line of the knee.

An adjustable plinth was used to support the nondominant leg at 45 degrees of hip flexion. The other

limb remained static in neutral. After 60 seconds in this position, the cuff was inflated to a pressure of 200 mm Hg. Cuff inflation was taken as time zero (Fig. 2). In the next 60 seconds, the participant was helped into standing and a backpack weighted to 40 kg was placed onto his or her back by the researcher (Fig. 2). This backpack provided the resistance for the submaximal exercise.

Twenty, timed repetitions of single-leg, heel-raising exercise were commenced with the nondominant leg. The participant was instructed to raise the heel when a pre-recorded tone sounded and relax the heel down when it ceased. The 20 repetitions were performed in time with tones of 2 seconds duration played on an audio track. Once completed, the backpack was removed and the participant stood on their nondominant lower limb for the remainder of the procedure.

### TENS Procedure

A NeuroTrac 3 TENS machine (Verity Medical Ltd, Surrey, UK) was used for electrical stimulation. A segmental electrode application was employed using self-adhesive carbon rubber electrodes measuring 5 × 5 cm (PhysioMed PALS electrodes, Glossop, UK). Electrode placement sites were determined depending on where the participant experienced pain during the familiarization session. The placement sites were always at least 2 cm apart and normally 1 proximal and 1 distal to the gastrocnemius muscle belly.

The TENS machine was calibrated before use with a digital recording oscilloscope and tested manually by the researcher before each testing session. Participants in the HF-TENS group were instructed that the intensity of stimulation must be "strong but comfortable" at all times and to report if the intensity faded during the experiment so that it could be adjusted. The display screen and control panel of the TENS unit were covered and not visible to the participant throughout the procedure. HF-TENS stimulation parameters delivered 200  $\mu$ s biphasic pulsed currents at 120 Hz in a "continuous" pulse pattern.

The P-TENS stimulation used the same TENS unit and programmed settings; however, undetectable breaks in the wires did not allow current to reach the participant. Participants in the P-TENS group were told that "different dosages of TENS were being tested, some of which might not cause any sensation to be felt."

### Ischemic Pain Measurement

Time (in seconds) to pain threshold, pain tolerance, and pain endurance were measured and analyzed as primary outcomes. Pain threshold is defined as "the least experience of pain which a subject can recognize."<sup>14</sup> In this study, pain threshold was explained to the participants as "the first moment discomfort turns to pain." Participants were instructed to report pain threshold by saying, "pain now."<sup>5,15</sup> Pain tolerance is defined as "the greatest level of pain which a subject is prepared to tolerate."<sup>14</sup> For the purposes of this study it was explained as "the moment you are no longer able to tolerate the pain." The participants were instructed to indicate this point by stating, "stop."<sup>5,15</sup> Pain endurance is defined as the time in seconds between pain threshold and pain tolerance.<sup>5</sup>

Pain intensity during ischemia was measured using a 21-point numerical rating scale (21-NRS): a numerical scale ranging from 0 to 20, with labels of "no pain" and "unbearable pain," respectively. The participant rated their pain at fixed, but irregular intervals of 30, 35, 40, or 45

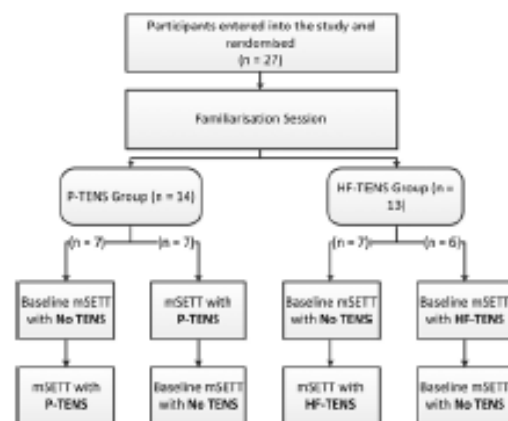


FIGURE 1. Diagram detailing testing session procedure and entry into the conditions in each group. HF-TENS indicates high-frequency transcutaneous electrical nerve stimulation; P-TENS, placebo TENS; mSETT, modified Submaximal Effort Youmiquet Test.



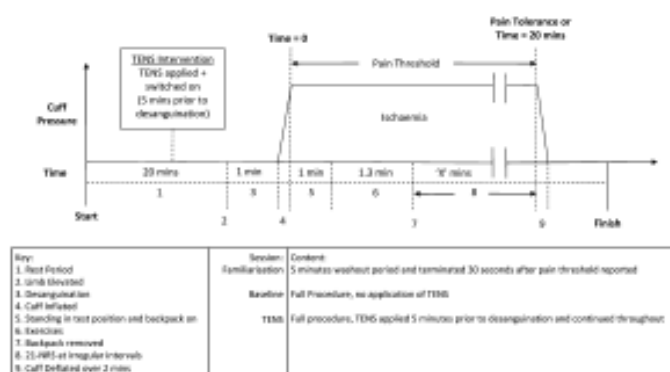


FIGURE 2. Modified Submaximal Effort Tourniquet Test procedure. 21-NRS indicates 21-point numerical rating scale; TENS, transcutaneous electrical nerve stimulation.

seconds. These irregular intervals were used to blind the participants to the time elapsed.

A MPQ<sup>16</sup> was administered retrospectively: within 5 minutes of the participant reporting 'pain tolerance' and the simultaneous release of the cuff. The participant was asked to describe the pain they experienced at pain tolerance. Pain Rating Index (PRI) scores from the MPQ provided a measure of the sensory, reactive, and total nature of the ischemic pain at the point of tolerance.<sup>2,16</sup>

### Statistical Analysis

All data are expressed as mean value  $\pm$  standard error. Paired *t*-tests were compared within-group scores for the mean time taken (in seconds) to report pain threshold and pain tolerance. The same analysis was used to compare pain endurance and PRI scores. For between-group comparison of pain threshold, tolerance, endurance, intensity, and PRI scores, the mean individual change in score from baseline was analyzed. Score at baseline for each participant was subtracted from the same participant's score with either the P-TENS or HF-TENS intervention. The group mean of these calculations was compared using independent *t*-tests. Statistical significance was set at  $P = 0.05$  (2-tailed). Analysis was performed using SPSS version 17.0.

## RESULTS

All 27 participants were included in the analysis [mean age (range) 27 (19 to 47) years; 16 male]. Groups were similar in terms of demographic data.

### Within-Group Profiles

#### Pain Threshold

Compared with the baseline, the mean time taken, in seconds, to report pain threshold increased with HF-TENS and P-TENS ( $123.1 \pm 7.3$  to  $151.9 \pm 9.6$  and  $127.6 \pm 5.9$  to  $133.7 \pm 5.4$ , respectively). The change, however, was only significant for HF-TENS ( $t(12) = 3.668$ ,  $P = 0.003$ ,  $r = 0.73$ ) (Fig. 3A).

#### Pain Tolerance

Compared with the baseline, both interventions increased the mean time to report pain tolerance: HF-TENS:  $383.7 \pm 19.8$  to  $584.5 \pm 32.9$  ( $t(12) = 5.397$ ,  $P < 0.001$ ,

$r = 0.84$ ); P-TENS:  $413.0 \pm 24.9$  to  $461.0 \pm 27.6$  ( $t(13) = 2.617$ ,  $P < 0.05$ ,  $r = 0.59$ ) (Figs. 3B).

#### Pain Endurance

Compared with baseline, both interventions also increased pain endurance:  $257.9 \pm 15.3$  to  $432.5 \pm 26.4$  with HF-TENS ( $t(12) = 5.082$ ,  $P < 0.001$ ,  $r = 0.83$ ) and  $285.4 \pm 24.0$  to  $327.3 \pm 25.5$  with P-TENS ( $t(13) = 2.427$ ,  $P < 0.05$ ,  $r = 0.56$ ) (Figs. 3C). Note that for the change in pain tolerance and pain endurance, the level of significance and effect sizes were greater in the HF-TENS group compared with the P-TENS group.

### Between-Group Differences

#### Pain Threshold

The independent *t*-test showed a significantly greater increase in mean time to pain threshold in the HF-TENS group ( $28.9 \pm 7.9$ ) compared with the P-TENS group ( $6.1 \pm 4.1$ ,  $t(18.070) = -2.565$ ,  $P < 0.05$ ,  $r = 0.52$ ) (Fig. 4A).

#### Pain Tolerance

The mean increase in pain tolerance with HF-TENS was found to be greater than with P-TENS ( $203.0 \pm 35.5$  and  $48.0 \pm 18.3$ , respectively,  $t(17.324) = -3.732$ ,  $P = 0.002$ ,  $r = 0.67$ ) (Fig. 4B).

#### Pain Endurance

The mean increase in pain endurance was also found to be greater with HF-TENS than with P-TENS ( $173.1 \pm 32.6$  and  $41.9 \pm 17.3$ ,  $t(17.617) = -3.479$ ,  $P = 0.003$ ,  $r = 0.64$ ) (Fig. 4C).

#### Pain Intensity

The baseline condition (mSETT-induced ischemic pain without TENS intervention) showed a similar pattern of increasing pain intensity over time in both groups, as measured with the 21-NRS (Fig. 5). All participants reached pain tolerance by 510 seconds. There was no significant difference between the groups.

Figure 6 shows the mean change in the reported pain intensity with HF-TENS and P-TENS interventions. Both HF-TENS and P-TENS groups showed a mean reduction in pain intensity, as indicated by the negative values

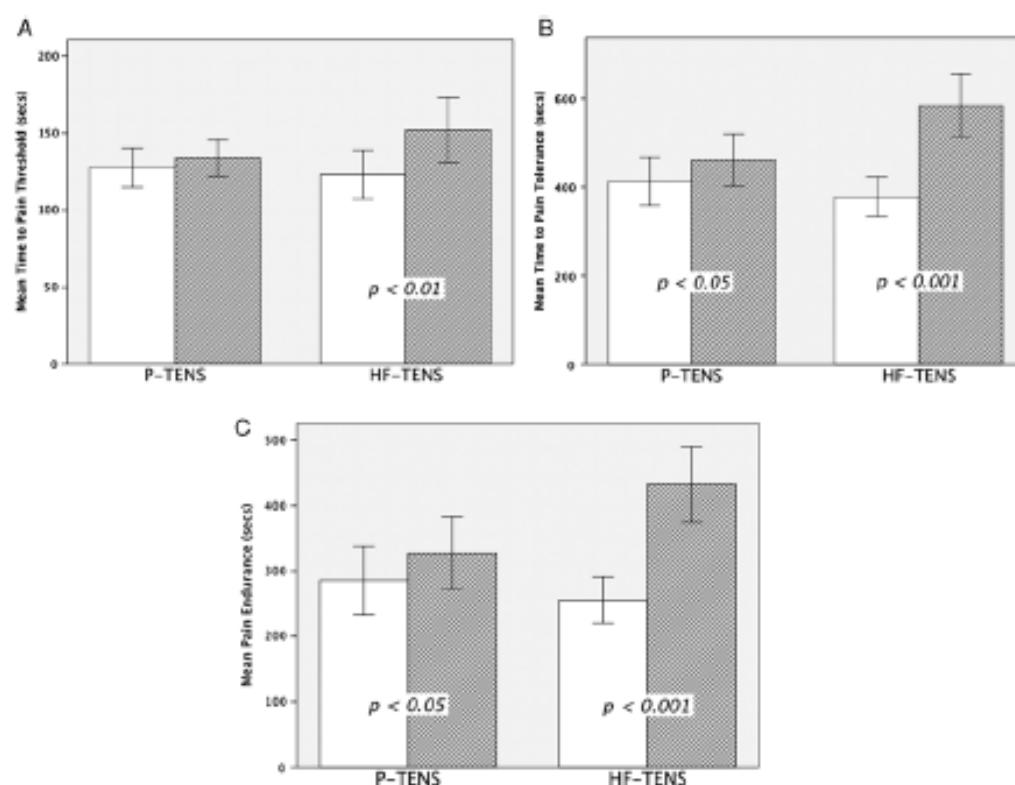


FIGURE 3. Graphs of mean time taken (seconds) to report (A) pain threshold, (B) pain tolerance, and (C) pain endurance for both groups. HF-TENS indicates high-frequency transcutaneous electrical nerve stimulation; P-TENS placebo transcutaneous electrical nerve stimulation. Open bars indicate baseline; shaded bars, intervention. Error bars = 95% confidence interval.

(Fig. 6). Participants in the HF-TENS group reported a greater reduction in 21-NRS scores throughout pain duration compared with P-TENS. Scores with HF-TENS intervention were significantly lower at 210 seconds, and from 320 to 510 seconds (ie, at 3½ min, and from approximately 5½ until 8½ min).

### Pain Quality

Table 1 details the Total MPQ-PRI, Sensory PRI, and Reactive PRI scores in the HF-TENS and P-TENS groups. Changes in PRI scores from baseline were found to be significant for Total MPQ-PRI and Sensory PRI in both groups. The only significant change in Reactive PRI was in the P-TENS group (Table 1). There were no between-group differences in PRI scores.

### DISCUSSION

This study used a novel mSETT methodology to induce ischemic pain in the lower limb. The results indicate that both HF-TENS and P-TENS reduced pain compared with baseline. However, when compared with P-TENS, HF-TENS delayed pain perception and pain tolerance for a longer duration; and lowered pain levels to a greater extent, over a longer period of time. HF-TENS therefore had a

greater impact on several aspects of the mSETT-induced pain experience than did P-TENS.

HF-TENS is proposed to act by activating large-diameter mechanoreceptors ( $A\beta$ -fibers),  $\delta$ -opioid receptors, and increasing levels of  $\gamma$ -aminobutyric acid.<sup>10,17,18</sup> This mechanism of action is associated with immediate, localized, segmental inhibition as conceived by the original Gate Control theory.<sup>17,19,20</sup> The hypoalgesic effects of HF-TENS observed in this study could be mediated through these mechanisms. As highlighted in Figure 3, HF-TENS had an immediate effect. The mean delay in the initial perception of pain in the HF-TENS group was 28.9 seconds, representing a 24% increase from baseline. Once pain was perceived, HF-TENS reduced the severity of the pain and increased the time it took participants to reach and report pain tolerance by 203.0 seconds—an increase of 52% compared with baseline. The effect of the delay in pain threshold and pain tolerance, and the reduction of pain intensity between these 2 points, was to extend pain endurance by 173.1 seconds, that is, 68% longer than baseline. These data, as shown in Figures 3 and 6, therefore indicate a physiological inhibition of perceived pain at pain threshold, during the minute-by-minute endurance of pain, and at the point of pain tolerance, that is, at 3 key points across the induced ischemic pain experience in volunteers.

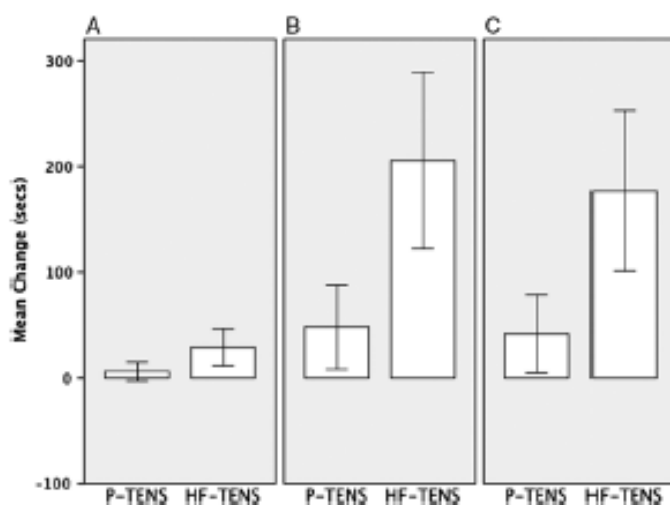


FIGURE 4. Graphs of mean change in time taken to report (A) pain threshold ( $P < 0.05$ ), (B) pain tolerance ( $P = 0.002$ ), and (C) pain endurance ( $P = 0.003$ ) in each group. Error bars = 95% confidence interval. HF-TENS indicates high-frequency transcutaneous electrical nerve stimulation; P-TENS placebo TENS.

Figure 5 shows the level of pain being experienced without any intervention. Induced lower limb ischemic pain increased steadily and gradually over time, in both groups. Figure 6 shows that when the interventions were applied, the P-TENS group reported mild reductions in mean pain scores throughout the period of induced pain. In contrast, HF-TENS showed a more extreme dip, and longer lasting reduction of mean pain scores over time. The reduction of mean pain intensity with HF-TENS was significantly greater than that with placebo at 7 points throughout the pain experience. Furthermore, as shown in Figures 5 and 6, the reduction in mean pain scores with HF-TENS was the greatest when pain intensity would normally have reached its highest levels had TENS not been applied, that is, from 290 to 510 seconds. Nevertheless, HF-TENS began to lose its capability to reduce pain by

approximately 675 seconds when the NRS scores show a sharp and sudden increase in intensity. The increase culminated in reports of pain tolerance shortly thereafter. These results suggest that spinal gating inhibition is strong when it is initially activated but that it remains strong over a relatively short period. The strength of the inhibition seems to be gradually overcome in the presence of an ongoing nociceptive input, in this case from cuff-induced ischemia. In our experiment, the ischemia was continuous throughout the average period of pain endurance of  $432.5 \pm 26.4$  seconds (approximately 7 min) (Figs. 3 and 6).

Table 1 shows the mean MPQ scores of intolerable pain reported retrospectively by participants completing their baseline and TENS trials. Significant reductions reported in sensory pain by the HF-TENS group, and in sensory and reactive pain by the P-TENS group contributed

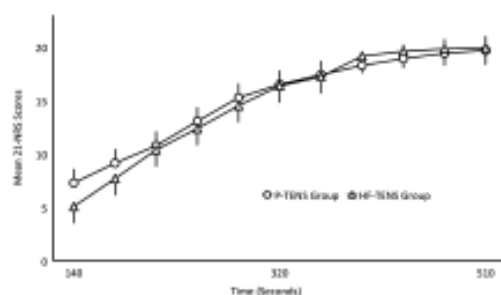


FIGURE 5. Graph of mean 21-point numerical rating scale (21-NRS) scores during modified Submaximal Effort Toumiquet Test without transcutaneous electrical nerve stimulation (TENS). 21-NRS scores increased steadily over time and levelled out before pain tolerance. HF-TENS indicates high-frequency TENS; P-TENS placebo TENS. Error bars = SE of mean.

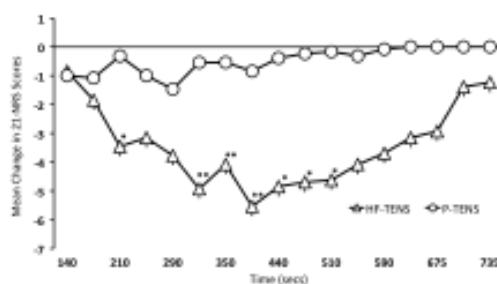


FIGURE 6. Graph of mean change in 21-point numerical rating scale (21-NRS) scores throughout the modified Submaximal Effort Toumiquet Test with high-frequency transcutaneous electrical nerve stimulation (HF-TENS) and placebo TENS (P-TENS) interventions. Significant difference between groups (\* $P < 0.05$ ; \*\* $P < 0.01$  independent *t* test (2-tailed)). Error bars = SE of mean.



TABLE 1. Mean PRI Scores for Both Groups on Completion of Baseline and TENS Intervention

		TPRI		SPRI		RPRI	
		Mean (SE)	P (r)	Mean (SE)	P (r)	Mean (SE)	P (r)
HF-TENS	Baseline	30.9 (3.2)		19.2 (1.7)		11.7 (1.7)	
	Intervention	24.6 (2.9)	0.005 (0.68)	15.1 (1.8)	0.0002 (0.74)	9.50 (1.4)	0.109 (0.45)
P-TENS	Baseline	27.4 (2.2)		15.9 (1.3)		11.5 (1.1)	
	Intervention	23.2 (1.8)	0.004 (0.70)	13.4 (0.98)	0.015 (0.61)	9.80 (0.96)	0.011 (0.64)

Significant difference indicated within groups Paired *t* test (2-tailed).

HF-TENS indicates high-frequency transcutaneous electrical nerve stimulation; P-TENS, placebo TENS; RPRI, Reactive Pain Rating Index score; SPRI, Sensory Pain Rating Index score; TPRI, Total Pain Rating Index score.

to significantly lower total MPQ scores of intolerable pain in both groups (Table 1). The application of both a placebo and active TENS (HF-TENS) seems to have lowered the level of participants' tolerance for pain.

Figure 6 shows that pain intensity measured with the NRS was modified in both HF-TENS and P-TENS conditions during the first two thirds of the period of pain endurance. The pain returned however to higher levels during the latter one third. In the case of HF-TENS, there was a dramatic resurgence in pain intensity over the latter 2 to 3 minutes, most likely as the inhibitory 'gating' is broken down. Participants in the HF-TENS condition may have found the resurgence of pain after a period of relatively mild pain to be intolerable, sooner than was the case in their baseline condition, thus accounting for lower MPQ scores of pain "tolerance." Only MPQ sensory pain scores were significantly reduced in the HF-TENS condition. This result, which was sufficient to significantly lower the mean total PRI score, suggests that the pain reduction obtained was a direct physiological effect of inhibitory gating.

Participants in the P-TENS group reported considerably less of a drop, and resurgence, of NRS pain scores than did the HF-TENS group. P-TENS pain levels dipped only slightly over the first 5 minutes of ischemic pain. They then remained at the same level for several minutes—a level that was reported as intolerable (Fig. 6). P-TENS participants believed they were being given a real treatment for their pain. The significant reduction in both the Sensory and Reactive MPQ scores in the P-TENS group suggests that a placebo effect, involving both physiological and psychological mechanisms of pain relief did occur,<sup>2,5,21,22</sup> and accounted for the significant reduction in the mean total PRI at pain tolerance in this group.

Overall, the results suggest that both physiological and psychological mechanisms of pain inhibition were activated by the application of TENS in this laboratory study. However, HF-TENS was found to be more effective.

The results of this experimental study using mSETT are in line with our previous results indicating delayed perception of pain and modified pain scores in induced lower limb ischemic pain using HF-TENS.<sup>11</sup> The results suggest replicability of the effect of HF-TENS on the mSETT. Furthermore, HF-TENS in both upper limb and lower limb induced ischemic pain, delays pain tolerance,<sup>1,2,6</sup> and decreases pain intensity, as measured with linear pain scales.<sup>1,2,6,10</sup> A recent study<sup>10</sup> showed that HF-TENS (vs. Low-Frequency TENS and P-TENS) reduced pain intensity during the first 2 minutes of induced upper limb ischemic pain. Our reported study is the first investigation of TENS on induced lower limb ischemic pain and it shows initial and extending reductions in pain intensity over sev-

eral more minutes than does the study by Chen and Johnson for the upper limb.<sup>10</sup>

Our results, shown over approximately 12 minutes of testing, have also suggested the potential utility of HF-TENS for the management of clinical ischemic pain in the lower limb. We are currently testing the effects of TENS in patients with Intermittent Claudication (IC) from peripheral arterial disease. IC is characterized by pain in the lower limb(s) and reduced walking performance during the first minutes of walking. The pain, which typically builds up over several minutes and stops or hinders patients from walking further, is due to decreased perfusion of the muscles and insufficient nutrient supply in the lower limbs when exercising, ie ischemia.<sup>23–25</sup> The results we present here on laboratory-induced ischemia in healthy volunteers suggest that HF-TENS may be a useful method of pain relief in patients with IC.

## CONCLUSIONS

The mSETT, used to induce lower limb ischemic pain, gave a detailed picture of the ischemic pain curve, and its inhibition, in healthy volunteers. HF-TENS modified 3 key aspects of the ischemic pain experience over time: pain threshold, pain tolerance, and pain endurance. HF-TENS also reduced pain intensity measured with a numerical pain scale during ischemia. Interestingly, it also lowered the psychological point at which participants reported intolerance of pain, as measured with an MPQ. This preliminary study on induced lower limb ischemia showed that HF-TENS had both physiological and psychological effects.

## REFERENCES

1. Woolf CJ. Transcutaneous electrical nerve stimulation and the reaction to experimental pain in human subjects. *Pain*. 1979;7:115–127.
2. Roche PA, Gijssels K, Belch JJP, et al. Modification of induced ischaemic pain by transcutaneous electrical nerve stimulation. *Pain*. 1984;20:45–52.
3. Walsh DM, Liggett C, Baxter D, et al. A double-blind investigation of the hypoalgesic effects of transcutaneous electrical nerve stimulation upon experimentally induced ischaemic pain. *Pain*. 1995;61:39–40.
4. Foster NE, Baxter P, Walsh DM, et al. Manipulation of transcutaneous electrical nerve stimulation variables has no effect on two models of experimental pain in humans. *Clin J Pain*. 1996;12:301–310.
5. Roche PA, Tan H-, Stanton WR. Modification of induced ischaemic pain by placebo electrotherapy. *Physiother Theory Pract*. 2002;18:131–139.
6. Johnson MI, Tabasam G. An investigation into the analgesic effects of interventional currents and transcutaneous electrical nerve stimulation on experimentally induced ischemic pain in otherwise pain-free volunteers. *Phys Ther*. 2003;83:208–223.



7. Smith GM, Ebert LD, Markowitz RA, et al. An experimental pain method sensitive to morphine in man: the Submaximal Effort Tourniquet Technique. *J Pharmacol Exp Ther*. 1966;154:324-332.
8. Moore PA, Duncan GH, Scott DS, et al. The submaximal effort tourniquet test: its use in evaluating experimental and chronic pain. *Pain*. 1979;6:375-382.
9. Staahl C, Drewes AM. Experimental human pain models: a review of standardised methods for preclinical testing of analgesics. *Basic Clin Pharmacol Toxicol*. 2004;95:97-111.
10. Chen C, Johnson MI. Differential frequency effects of strong nonpainful transcutaneous electrical nerve stimulation on experimentally induced ischemic pain in healthy human participants. *Clin J Pain*. 2011;27:434-441.
11. Roche PA, Santos D, Snijder J, et al. A model of ischemic pain in the calf and TENS modification of lower limb pain: preliminary results in: World Physical Therapy 2007 — Abstracts. *Physiotherapy*. 2007;93:S52.
12. Seenan C, Santos D, Snijder J, et al. Early Development of a Lower Limb Ischaemic Pain Test in Healthy Volunteers using the McGill Pain Questionnaire. *Proceedings of the 12th World Congress on Pain*. Castro-Lopez J, ed. IASP Press; Seattle; 2008.
13. Baxter D, Bazin S, Diffy B, et al. *Guidance for the Clinical Use of Electrophysical Agents*. London, UK: Chartered Society of Physiotherapy; 2006.
14. Merskey H, Bogduk N. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. Seattle: IASP Press; 1994.
15. Melzack R, Wall PD. *The Challenge of Pain*. Middlesex: Penguin; 1996.
16. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain*. 1975;1:277-299.
17. Sluka KA, Walsh D. Transcutaneous electrical nerve stimulation: basic science mechanisms and clinical effectiveness. *J Pain*. 2003;4:109-121.
18. DeSantana JM, Walsh DM, Vance C, et al. Effectiveness of transcutaneous electrical nerve stimulation for treatment of hyperalgesia and pain. *Curr Rheumatol Rep*. 2008;10:492-499.
19. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*. 1965;150:971-979.
20. Andersson SA, Holmgren E. Analgesic effects of peripheral conditioning stimulation. III. Effect of high frequency stimulation; segmental mechanisms interacting with pain. *Acupunct Electro-Ther Res*. 1978;3:23-36.
21. Amantio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. *J Neurosci*. 1999;19:484-494.
22. Amantio M, Pollo A, Maggi G, et al. Response variability to analgesics: a role for non-specific activation of endogenous opioids. *Pain*. 2001;90:205-215.
23. Bendermacher BL, Willigendael EM, Teijink JA, et al. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev*. 2006;2:CD005263.
24. Stewart KJ, Hiatt WR, Regensteiner JG, et al. Medical progress: exercise training for claudication. *New Engl J Med*. 2002;347:1941-1951.
25. Momen AH, Jensen MB, Norager CB, et al. Drug therapy for improving walking distance in intermittent claudication: a systematic review and meta-analysis of robust randomised controlled studies. *Eur J Vasc Endovasc Surg*. 2009;38:463-474.

# McGill Pain Questionnaire Descriptions of Lower Limb Ischaemic Pain in Clinical and Laboratory Settings (PT 057)

Chris Seenan<sup>1,2</sup>, Patricia Roche<sup>4</sup>, Chee-Wee Tan<sup>3</sup>, Steve McSwiggan<sup>3</sup>, Jill Belch<sup>3</sup>, Tom Mercer<sup>2</sup>

<sup>1</sup>School of Health and Life Sciences, Glasgow Caledonian University; <sup>2</sup>School of Health, Queen Margaret University; <sup>3</sup>Institute for Cardiovascular Research, University of Dundee; <sup>4</sup>Division of Applied Health Sciences, University of Aberdeen

## WHAT WE LEARNED

Lower limb ischaemic pain induced with the modified Submaximal Effort Tourniquet Test (mSETT) provides an adequate representation of Intermittent Claudication (IC) pain.

### INTRODUCTION

Intermittent Claudication (IC) is ischaemic pain in the lower limb and the cardinal symptom of Peripheral Arterial Disease (PAD). IC presents as disabling pain while walking, there is a dearth of literature regarding analgesic interventions.

A model of induced ischaemic pain in the lower limb of volunteers with was developed (mSETT, Seenan et al 2012). We employed the McGill Pain Questionnaire (MPQ) to compare volunteers' descriptions of pain with those from patients with IC.

The analysis sought similarities and differences in the pain experienced, as measured by the McGill Pain Questionnaire (MPQ). If comparable, the laboratory model could be used for testing analgesic interventions for IC.

### OBJECTIVE

Compare clinical and laboratory descriptions of ischaemic pain in the lower limb.

### METHODS

Sixty-three participants were recruited to a study of clinical or laboratory ischaemic pain in the lower limb (Table 1).

- Patients with IC (Group A) completed a standardised treadmill test.
- Healthy volunteers (Group B) completed a modified Submaximal Effort Tourniquet Test (mSETT) (200mmHg cuff around the thigh and submaximal effort exercise) (Roche et al 2007; Seenan et al 2012).
- All participants completed the MPQ vocabulary 5 minutes after testing.

Table 1: Participant demographics and overall Number of Words Chosen (NWC) and MPQ scores

	n	Mean Age (range)	Mean NWC	Mean Pain Rating Index (PRI)		
				Total	Sensory	Reactive
Clinical (Group A)	36	68 (53-85)	9.6	21.3	18.5	6.8
Laboratory (Group B)	27	26 (18-45)	11.4	29	17.7	11

Table 2: Classification of MPQ Subclass and made word chosen in subclasses with >50% utilisation for both groups. Note the higher rank of word chosen in Group B for subclasses 1, 9, 11 and 16.

MPQ Subclass	Group A	Group B
<b>Sensory</b>		
1. Tapping	Pricking (4)	Pricking (8)
5. Compressive Pressure	Crampling (4)	Crampling (4)
9. Suffocation	Asphyxiation (10)	Heavy (16)
<b>Affective</b>		
11. Tension	Striving (11)	Exhausting (12)
<b>Evaluative / Miscellaneous</b>		
16. Evaluative	Troublesome (12)	Unbearable (5)
18. Sensory-Miscellaneous	Tight (11)	Tight (11)
20. Affective-Evaluative-Miscellaneous	Nagging (11)	Nagging (11)

### RESULTS

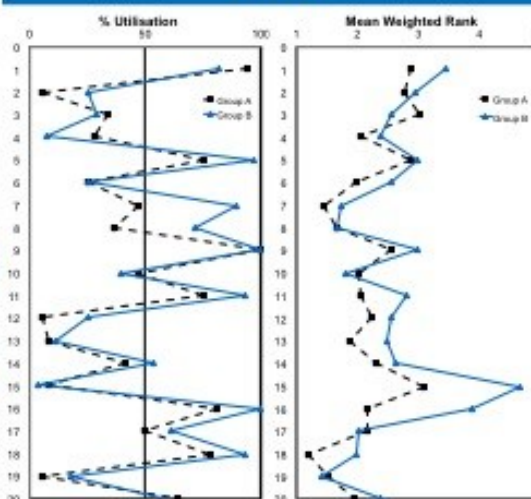


Figure 1: Percent utilisation of MPQ categories in Group A and B. Table 2 displays the details of the subclasses with >50% utilisation by both groups.

- Mean Number of Words Chosen (NWC) and subclass utilisation was similar in both groups (Table 1 and Figure 1).
- There were 11 subclasses with more the 50% utilisation in either group. Of these, 7 were common between the groups (Figure 1 and Table 2). The most commonly chosen adjective in these subclasses was also similar (Table 2).
- Despite these similarities, Group A had lower Total Pain Rating Index (PRI) scores than Group B. Mean (SD) Group A = 21.3 (7.9), Group B = 29.0 (9.7),  $t(62) = 3.517$ ,  $p = .001$ , 95% CI = 3.3-12.2,  $r = .41$ .
- This difference in PRI scores can be explained by the higher rank of word chosen by Group B participants for the majority of subclasses (Figure 2 and Table 2).

### DISCUSSION

This study provides the first comparison of clinical and experimental ischaemic pain in the lower limb.

Similarities in descriptive quality were:

- The number of words were used to describe the experiences
- The same seven subclasses were selected >50% of the time by participants in both groups
- Of these categories:
  - 3 were sensory (aching, throbbing and cramping)
  - 1 was affective (tiring)
  - 3 were evaluative-miscellaneous (troublesome, tight and nagging)

A difference was that volunteers with induced ischaemic pain showed generally higher percent use, and rank use, of the subclasses than did patients with IC (Figures 1 and 2, Table 2).

The sensory words selected by each group suggests both nociceptive and neuropathic pain (Wilkie et al 2001).

The higher ranks chosen by the laboratory subjects may be related to a greater degree of attention to the pain compared with patients with IC, who have everyday leg pain. Alternatively, laboratory subjects may have experienced a more intense pain stimulus due to the induction of pain with an ischaemic cuff.

The mSETT induces a pain experience that is comparable to that reported by patients with IC. With further refinement and exploration, the mSETT may prove to be a useful laboratory model of lower limb, clinical ischaemic pain.

### REFERENCES

- Roche PA, Seenan C, Seenan J, et al. 2007. A model of ischaemic pain in the calf and TENS modulation of lower limb pain: preliminary results in. *North Physical Therapy* 2007 — Abstracts, *Physiotherapy*, 95, pp 952.
- Seenan, C., Roche, PA, Tan, CWL, Mercer, T. 2012. *article in press*, Identification of Experimental Lower Limb Ischaemic Pain with Tourniquet-Induced Ischaemic Pain. *Clinical Journal of Pain*, *28*, pp 100-108.
- Wilkie, D.J., Huang, H.Y., Kelly, M., Clark, K.C. 2001. Nociceptive and Neuropathic Pain in Patients with Long Latency Latency in Comparison of Pain Quality Descriptors. *Journal of Pain and Palliative Care*, 2001, pp 100-108.

# Transcutaneous Electrical Nerve Stimulation (TENS) and Treadmill Walking Performance in patients with Intermittent Claudication (IC): A Proof of Concept Study

Chris Seenan<sup>1,2</sup>, Steve McSwiggan<sup>3</sup>, Patricia Roche<sup>4</sup>, Chee-Wee Tan<sup>2</sup>, Tom Mercer<sup>2</sup>, Jill Belch<sup>3</sup>

<sup>1</sup>School of Health and Life Sciences, Glasgow Caledonian University; <sup>2</sup>School of Health, Queen Margaret University; <sup>3</sup>Institute for Cardiovascular Research, University of Dundee; <sup>4</sup>Division of Applied Health Sciences, University of Aberdeen

## WHAT WE LEARNED

**Distance walked to perception and tolerance of pain increased with TENS intervention. There was no difference in overall pain intensity reported. Heart Rate at perception and tolerance of pain increased with TENS.**

### INTRODUCTION

- TENS has been shown to be an effective intervention for painful conditions.
- Intermittent Claudication (IC) is a chronic pain condition and the cardinal symptom of Peripheral Arterial Disease (PAD).
- IC pain is related to ischaemia in the lower limb(s) and manifests as a 'cramping' pain while walking.<sup>1</sup>
- Currently, there are no interventions for the symptomatic management of IC pain.
- TENS has been shown to be effective in reducing experimental, lower limb ischaemic pain but it has not been tested for IC pain.<sup>2</sup>

### OBJECTIVE

To investigate the effects of TENS on treadmill walking distance and measures of pain in patients with PAD and IC

### METHODS

- Thirty six patients with PAD and IC completed a standardised treadmill test (2mph, 0% gradient with 2% increase every 2 minutes) on two separate occasions.<sup>3</sup>
- Initial, Functional and Absolute Claudication Distance (ICD, FCD and ACD) and Heart Rate at these points were compared along with Pain Rating Index (PRI) scores of the McGill Pain Questionnaire (MPQ), using a within-subject design.

### RESULTS

- Median ICD, FCD and ACD increased with TENS (Table 1 and Figure 1).
- No difference was observed between median PRI scores (Table 1)
- Mean Heart Rate at ICD and ACD increased with TENS (Table 1 and Figure 2).

Table 1: Median (range) treadmill walking distance (m); Median (range) PRI scores and Mean (SE) Heart Rate (HR) at ICD and ACD with placebo and active TENS. (p values for treadmill distance and PRI = Wilcoxon Signed Ranks test; p values for HR = paired t-test)

	ICD	FCD	ACD	PRI	HR ICD	HR ACD
Placebo TENS	74 (22-271)	156 (70-545)	179 (99-806)	22 (2-38)	99 (3.0)	115 (3.8)
Active TENS	81 (34-385)	164 (79-654)	212 (113-762)	22 (2-41)	103 (2.7)	122 (3.5)
p	.041	.044	.003	.405	.014	.000

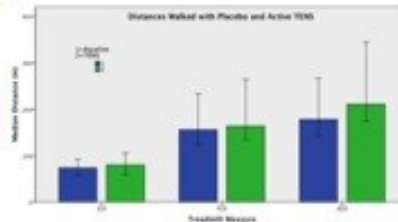


Figure 1: Median treadmill measures with placebo and active TENS. Baseline = Placebo TENS. (Error Bars = 95% CI)

Key:  
ICD = Initial Claudication Distance (distance to pain threshold)  
FCD = Functional Claudication Distance (distance to functional pain tolerance)  
ACD = Absolute Claudication Distance (distance to absolute pain tolerance)

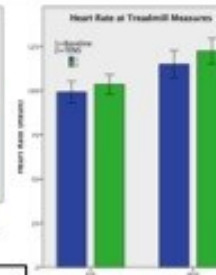


Figure 2: Mean Heart Rate at ICD and ACD with placebo and active TENS. Baseline = Placebo TENS. (Error Bars = 95% CI)

### CONCLUSIONS

- TENS increased treadmill walking distance in patients with IC however, no reduction in overall pain intensity was reported
- This indicates that TENS delays perception and tolerance of IC pain, thus increasing distance walked
- TENS was associated with an increase in heart rate at pain threshold and tolerance
- This indicates an increase in cardiovascular effort achieved with TENS (the primary aim of exercise therapy in PAD and IC)
- TENS could be a useful adjunctive intervention for increasing walking distance in patients with PAD and IC

### Next Steps

- Investigate the patient experience of using TENS at home for PAD and IC
- RCT of the effects of TENS on treadmill walking performance for patients with PAD and IC
- Longitudinal RCT of TENS on physical activity and CV outcomes in patients with PAD and IC

### REFERENCES

- Bendemeier DL, Willgerodt JM, Taylor JA, et al. (2006) Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. Cochrane Database Systematic Review. 1st 2nd, 2006
- Seenan C, Roche P, Tan C, Mercer T. (2012) Modification of Experimental Lower Limb Ischaemia Pain with Transcutaneous Electrical Nerve Stimulation. Clinical Journal of Pain. Vol 28 (4) 300-308
- Gerber K, Seenan C, Mercer T, Smith L, Smith L. (2011) Progressive vs single-stage treadmill tests for evaluation of claudication. Medicine and Science in Sports and Exercise. Vol 23, pp652-658



# 'Grin and bear it': patients' experiences of living with Intermittent Claudication (IC) and using Transcutaneous Electrical Nerve Stimulation (TENS)

Chris Seenan<sup>1,2</sup>, Linda Orr<sup>3</sup>, Steve McSwiggan<sup>3</sup>, Patricia Roche<sup>4</sup>, Chee-Wee Tan<sup>2</sup>, Tom Mercer<sup>2</sup>, Jill Belch<sup>3</sup>

<sup>1</sup>School of Health and Life Sciences, Glasgow Caledonian University; <sup>2</sup>School of Health, Queen Margaret University; <sup>3</sup>Institute for Cardiovascular Research, University of Dundee; <sup>4</sup>Division of Applied Health Sciences, University of Aberdeen

## WHAT WE LEARNED

The patient experience of living with PAD and IC is characterised by feelings of frustration. Patients with PAD and IC expressed a positive experience of using TENS at home however, treatment expectations need to be carefully managed.

### RESEARCH QUESTIONS

- What characterises the patient experience of living with PAD and IC?
- What characterises the patient experience of using TENS in daily life for IC?

### BACKGROUND

- The patient experience of living with Peripheral Arterial Disease (PAD) and Intermittent Claudication (IC) has not been fully described in the literature.<sup>1</sup>
- Previous studies found that Transcutaneous Electrical Nerve Stimulation (TENS) reduces experimental ischaemic pain in the lower limb and increases treadmill walking performance in patients with PAD and IC.<sup>2,3</sup>
- The experience of using TENS in daily life in this patient population has not been investigated.

### METHODS

- Six patients with stable PAD and IC were provided with a TENS unit, training and instructions to use it independently for one month
- A focus group discussion held at the end of the month elicited participants' experiences of living with the disease and using TENS
- The transcribed text was analysed using manifest and latent content analysis

### REFERENCES

1. Ramanathan, C., Jelliffe, J.R., Alcock, J.R., Anderson, E. (2008). The patient experience of intermittent claudication: a review of the literature. *Journal of Vascular Medicine and Biology*, 20(4), 201-208.
2. Seenan, C., Roche, P.A., Orr, L., McSwiggan, S. (2015). The effect of Transcutaneous Electrical Nerve Stimulation (TENS) on walking performance in patients with Intermittent Claudication (IC). *Journal of Vascular Medicine and Biology*, 27(4), 201-208.
3. Seenan, C., McSwiggan, S., Roche, P.A., Orr, L., McSwiggan, S. (2015). The effect of Transcutaneous Electrical Nerve Stimulation (TENS) on walking performance in patients with Intermittent Claudication (IC). *Journal of Vascular Medicine and Biology*, 27(4), 201-208.

### PRELIMINARY FINDINGS

#### Living with PAD and IC

"you're walking and the pain is there, you stop walking and you sit down, 2 minutes and it's gone ... what the hell is going on here? ... it is frustrating, very frustrating" P4

"to come and do something, the first thing you think of is how much walking is involved ... and will I just be a damned nuisance if I go because I will be trailing back and behind the others ... and you just don't go" P2

"(P4) it is, they keep saying 'grin and bear it' and that's all I have been doing for years and years now ... (P5) yeah, me too, the very same. I'm just like, it will be 5 years, maybe 6 years I have had it and you just have to put up with it"

"that's what puzzling me all these years ... I keep saying to the surgeon and all that and they said ... we don't know what the problem is so all this is probably helping" P4

#### Using TENS for IC

"I still had it (the pain) but it was a different form of pain ... it was sort of numbing, not so sore but it was still there" P3

"if I didn't have the TENS and this particular course I'm thinking, I could never get round that course without stopping and having to shake my leg and wait a minute which becomes quite embarrassing" P1

#### Emerging Themes

The experience of living with PAD and IC was found to be characterised by feelings of **frustration**.

This was interpreted through the following themes:

- 'transient, yet chronic pain'
- 'lifestyle limitations'
- 'knowledge and understanding'
- 'grin and bear it'

The experience of using TENS in daily life was characterised by both **benefit** and **disappointment**.

This was interpreted through the following themes:

- 'masking, but not taking the pain away'
- 'walking further, but not far enough'

### CONCLUSIONS

- The experience of living with PAD and IC is characterised by feelings of frustration, helplessness, fear and social isolation.
- TENS is a possible adjunctive intervention for patients with PAD and IC however, when delivered it should be accompanied by education and discussion of expectations



The study was conducted in accordance with the Declaration of Helsinki and approved by the Local NHS Ethics Committee (Reference Number 10/51452/57). Written informed consent was obtained from all participants before inclusion.

Chris Seenan was the recipient of a Queen Margaret University PhD Bursary and this research was conducted at the Institute of Cardiovascular Research, University of Dundee

Chris Seenan  
School of Health and Life Sciences  
Glasgow Caledonian University  
G4 0BA  
Email: chris.seenan@gcu.ac.uk  
Phone: 0141 331 8701



Abstract:  
2216

# Early development of a Lower Limb Ischaemic Pain Test in healthy volunteers using the McGill Pain Questionnaire

Seenan C, Roche PA, Santos D, Calcraft J, Weddell A  
School of Health Sciences, Queen Margaret University, Edinburgh, UK

## Introduction and Aims

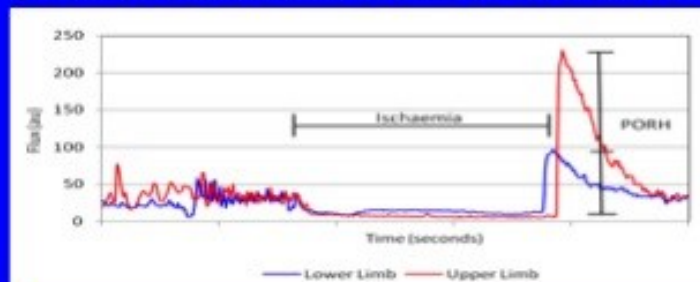
A laboratory method of induced lower limb ischaemia in healthy volunteers may help inform studies into the pain of intermittent claudication in patients with peripheral arterial disease. This preliminary study adapted the Submaximal Effort Tourniquet Test (SETT) technique of inducing upper limb ischaemia to a lower limb application. The study aims were: to compare measures of microcirculation, pain intensity and pain description between lower limb (LL) and upper limb (UL) applications in healthy volunteers.

**Subjects** Ten healthy male students participated.

## Methods

A within subjects cross-over study applied a modified SETT procedure to the upper and lower limbs (200mmHg cuff pressure; 20 repetitions of 50% maximal grip strength in the upper limb; 50% maximal plantar flexion strength in the lower limb). Laser Doppler Flowmetry (LDF) measured the Post-Occlusive Reactive Hyperaemic Response (PORH) - a measure of ischaemia in peripheral microcirculation. Subjects made a first report of 'pain', rated their pain intensity (21-NRS) every minute up to their report of 'pain tolerance', or when 20 minutes had elapsed. A McGill Pain Questionnaire (MPQ) was administered 5 minutes retrospectively, with subjects describing their pain at 'pain tolerance'.

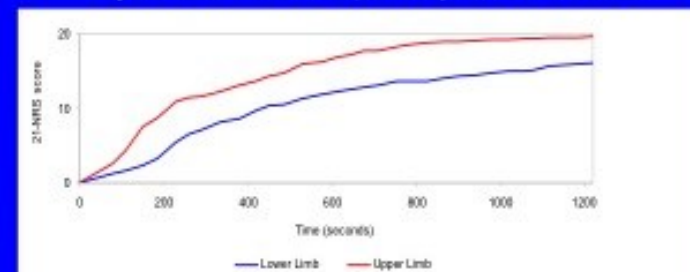
Figure 1: Induced ischaemia and the difference in PORH between the LL and UL measured with LDF



## Results

The PORH indicated ischaemia in both LL and UL but a lower level of ischaemia in LL ( $p=0.002$ ,  $t=9.802$ , (two-tailed), 95% CI). NRS scores increased steadily over time in both the LL & UL, however, mean LL NRS scores were lower than UL throughout ischaemia, reaching significance from 600 seconds onwards ( $p=.031$ ,  $z=-2.2$ , (two-tailed) 95% CI). The same MPQ sub-classes were chosen by 60% of subjects to describe both the LL and UL pain. Lower ranks of pain adjectives were chosen to describe LL pain compared with UL pain, resulting in a lower Pain Rating Index (PRI) ( $p=.012$ ,  $z=-2.5$ , (two-tailed) 95% CI).

Figure 2: Gradual increase in mean pain intensity over time in the LL and UL.



## Discussion and Conclusions

The adapted LL SETT induced tissue ischaemia as shown by LDF. Subjective descriptions of pain were similar in the LL and UL in their pattern of development and quality. However LL pain was less intense than the well-validated UL SETT. The LL application of SETT shows promising results but requires further refinement as a laboratory model of ischaemia in the calf muscle in volunteers.